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CORONARY ENDARTERITIS IN ACUTE RHEUMATISM

BY

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Various observers have described intimal changes in the coronary arteries of the heart in acute rheumatism.

Krehl[1], in 1890, was the first to note the occurrence of fibrous intimal thickening in the smaller arteries of the heart in chronic valvular disease of rheumatic origin. Later Romberg[2] drew attention to this intimal thickening and also reported the finding of hyaline thrombi in many of the small arteries of the heart in two cases of acute rheumatism. No change was found in the walls of the thrombosed vessels nor in the tissues surrounding them, and the presence of fissures between the thrombus and the vessel wall showed that the vascular occlusion was sometimes incomplete. Romberg's comment on the absence of muscle tissue infarction in relation to the occluded arteries was that either the hyaline thrombi formed just before death or that the good collateral blood supply of the myocardium prevented muscle necrosis.

Rabé[3], in an examination of the heart of a child, aged five, who died of rheumatic fever, found proliferative endarteritis accompanied by medial degeneration (mésartérite) in the small and medium sized coronary arteries. Aschoff[4, 5], who has shown that the walls of the small coronary arteries are sometimes involved in the inflammatory nodules which are named after him, has stated that most of the scars in the rheumatic myocardium are due to ischaemic necrosis caused through the consequent sclerotic narrowing of such vessels. Takayasu[6], who examined the heart of a girl, aged eight, dying of acute rheumatism, found what he described as canalized emboli in many of the small coronary arteries at or near the apex. These emboli were considered by Takayasu to have come from the vegetations on the valves of the heart.

Geipel[7], in 1909, reported a case of acute rheumatism in which there was marked endarteritis of the small and medium sized coronary arteries. Stenosis or complete occlusion, through the presence of fibrin masses and proliferated endothelial and subendothelial cells in the vascular lumen, was frequently noticed and some small infarcts in the myocardium were attributed to this. Geipel considered that the fibrin masses were in the nature of emboli derived from the vegetations on the heart valves and that the intimal changes were secondary to the embolic plugging of the vessel.

Coombs[8] has described the endothelial and subendothelial cell proliferation which so frequently occurs in the myocardial capillaries and arterioles, and has further remarked on the fibrous intimal thickening so often to be seen in the smaller and some of the larger coronary arteries in rheumatic carditis, an observation recently confirmed by Perry[9].

Wätjen[10], in his examination of a case of rheumatic myocarditis, found that all the layers of the coronary artery wall could be involved in the territory of the specific inflammatory nodules, and that nodules occurring in the intima destroyed the internal elastic lamina and involved, more or less strongly, the media. In other instances a diffuse eosinophil cell infiltration of the intima without recognizable nodule formation was observed. The lumen of vessels affected in this way was either

partly or quite filled with fresh thrombus masses or fresh or old organized tissue. Wätjen was of the opinion that this obliterative process in the vascular lumen was caused by the changes in the vessel wall and was not embolic in nature.

Pappenheimer and Von Glahn[11], who have described certain lesions in the intima of the aorta which they consider to be of rheumatic origin, found in one of their cases similar changes in the intima of a coronary artery. In their examination of the heart of a boy aged fifteen who died of acute rheumatism the intima of the left coronary artery close to its orifice was found to be represented by a loose tissue apparently derived from the endothelium together with a few wandering cells, including a fair number of polymorphonuclears.

Klinge and Vaubel[12], who believe that the initial change in the rheumatic lesion is a fibrinoid transformation of the ground substance of the connective tissue and that this is followed by cellular proliferation and infiltration, have shown that the intima of the small coronary arteries may be thus affected.

Present investigations.

The purpose of this report, which deals with the histological examination of the coronary arteries of four patients dying of acute rheumatism, is to present further evidence of the occurrence of a specific type of coronary endarteritis in rheumatic disease of the heart. Mention will first be made of the intimal age changes which take place in these vessels, since there is reference to them in the descriptions which follow.

Intimal age changes in the coronary arteries.—The coronary intima, which consists at birth of the internal elastic lamina covered by endothelium, begins in early life to undergo various structural alterations which lead to progressive thickening. An inner layer of elastic tissue called the boundary stripe layer splits off from the internal elastic lamina and between these two elastic boundaries there develops a longitudinal musculo-elastic layer of tissue into which medial muscle cells pass, through gaps which appear in the internal elastic lamina. Internal to the stripe there forms a circular layer of fibrous tissue which is rich in elastic fibres and is called the elastic hyperplastic layer. These two layers gradually increase in thickness and, as age progresses, a third layer appears internal to the elastic hyperplastic layer. This innermost layer is composed for the most part of collagenous fibres and is called the fibrous layer.

Wolkoff[13], who has made a study of the structure of the coronary arteries of normal hearts at different age periods, considers that this process of intimal thickening is much more marked in these arteries than in the other arteries in which age changes have been described. At the age of seven years, according to Wolkoff, the intima of the main coronary stems may be half as thick as the media, while at eighteen years the three layers may be present, the intima then being as thick as or thicker than the media. This thickening occurs in small areas at first but after the thirtieth year it affects the whole circumference of the vessel. In the medium-sized and smaller coronary branches similar changes occur but at correspondingly latter ages.

Wolkoff observed no intimal changes in the smaller myocardial arteries, but Gross[14] and his co-workers have recently shown that these also undergo somewhat similar age period changes which bring about intimal thickening.

Case histories and autopsy records.

Case 1.—Female, aged 8 years, who was admitted with rheumatic heart disease and attacks of severe abdominal pain with vomiting. Signs of fluid in the pericardium were detected a week after admission. During the first twelve days in hospital there were ten attacks of pain in the epigastrium. Each attack of pain lasted from five to ten minutes and was accompanied by vomiting. Later these attacks of pain became less frequent but increased in number again in the last few days before death, which occurred a month after admission. The temperature varied from 100° F. to 101° F. until a week before death when it dropped and remained at 99° F., with a drop to subnormal just before death. The blood Wassermann test was negative.

PREVIOUS HISTORY. When four years old the child complained of pains in the elbows and knees. These pains disappeared after some months and her health remained apparently good until about the age of seven-and-a-half years, when the parents noticed twitchings of the face and jerkings of her head, arms and legs. Later she complained of pain in the knee joints and when brought to hospital was admitted with a diagnosis of rheumatic arthritis, carditis and chorea. At the end of six weeks her condition had much improved and she was discharged to attend, but was readmitted three weeks latter on account of the sudden onset of attacks of severe abdominal pain and vomiting.

FAMILY HISTORY. There are two other children in the family, a boy of six with rheumatic heart disease and a boy of three who is apparently quite healthy. The parents are in good health and have no history of rheumatism or specific disease, and in each case the blood Wassermann test was negative.

AUTOPSY RECORD. The pericardial sac was markedly distended with turbid yellowish fluid showing the following cell count: polymorphs 40 per cent., lymphocytes 23 per cent., endothelials 37 per cent. No micro-organisms were seen in the direct smears made from this fluid and all cultures remained sterile. A thin fibrinous exudate was present on the surface of the visceral and parietal pericardium, more marked around the base of the heart. Hypertrophy and dilatation of the heart was found with thrush-breast appearance all over the inner surface of both ventricles. Rheumatic endocarditis of the mitral, tricuspid and aortic valves was present. Cultures made from the vegetations remained sterile. A fair amount of yellow fluid was found in the peritoneal and pleural cavities. There was chronic venous congestion of the viscera and moderate fibrosis of all heart-valve leaflets.

Case 2.—Male, aged 9 years, was admitted with pericarditis. He had always been a weakly child and during the six months previous to admission had suffered from frequent attacks of pain in the chest and abdomen with headache and vomiting. These attacks occurred at intervals during periods which lasted from one to two weeks. The last illness was of a similar nature but the symptoms were much more severe. Death took place nine days after admission. The blood Wassermann test was negative.

AUTOPSY RECORD. Fibrinous pericarditis was present, the pericardial layers being adherent but easily separated. Rheumatic endocarditis of the mitral, aortic, and tricuspid valves was found but no obvious fibrosis of the valve leaflets. There was a little clear yellow fluid in the pleural cavities and chronic venous congestion of the viscera. Cultures made from the vegetations on the heart valves remained sterile.

Case 3.—Female, aged 15 years, was admitted to the surgical ward for erysipelas of the face. The erysipelas cleared up in a few days and she was then transferred to the medical ward on account of the condition of her heart, which was diagnosed as rheumatic heart disease. She was discharged improved at the end of two months but was readmitted six weeks later with oedema of the feet and legs and a fibrillating heart. She died two days after admission. There was a history of an attack of acute rheumatic fever at the age of eleven. The blood Wassermann test was negative.

AUTOPSY RECORD. There was hypertrophy and dilatation of the heart with an adherent pericardium and rheumatic endocarditis of the mitral and aortic valves. The mitral valve leaflets were fibrosed and there was a moderate stenosis of the valvular orifice. Much clear yellow fluid was present in the peritoneal and pleural cavities. There was chronic venous congestion of the viscera. Cultures made from the vegetations on the heart valves remained sterile.

Case 4.—A female, aged 27 years, was admitted in an acutely ill condition with pericarditis and oedema of the feet and ankles. Death occurred twenty-four hours later. Eighteen weeks previous to admission the patient had a severe quinsy from which she never quite recovered and six weeks after the onset of the quinsy her condition was diagnosed as acute rheumatic fever. She was confined to bed and became progressively worse. There was no previous history of rheumatism. The blood Wassermann test was negative.

AUTOPSY RECORD. There was a large dilated heart with rheumatic pericarditis and endocarditis of the mitral and aortic valves and wall of the left auricle. Much clear yellow fluid was present in the peritoneal and pleural cavities. The lungs and liver showed chronic venous congestion. The spleen was double the normal size, and the cut surface showed a firm hyperplastic pulp. There was cloudy swelling only of the kidneys. Cultures made from the vegetations on the heart valves and the auricle wall remained sterile.

Histological examination.

There were numerous Aschoff nodules in the myocardium in all four cases but the outstanding feature was the condition of the coronary arteries. These showed a characteristic type of intimal inflammation with or without involvement of the media and some degree of periarteritis. The lesions were not necessarily nodular in distribution but might involve long stretches of the vessel, although in places there might be some variation in the intensity of the inflammatory reaction.

In case 1 both main coronary stems and many of their branches even to the smallest twigs were affected, the left coronary to a much greater extent than the right. In case 2 the condition was present in the main stem and some of the branches, both large and small, of the left coronary artery only, while in case 3 and 4 only a few of the smaller arteries in the wall of the left ventricle and in the basal third of the interventricular septum were affected. The histological picture of these vascular lesions corresponded with that generally recognized as the tissue reaction to the presence of the virus of acute rheumatism, namely, the Aschoff nodule.

In the precapillaries and the small arterioles the endothelium was raised up into the lumen through the deposition of fibrin in the subendothelial space. Sometimes this fibrin was more abundant at one point so that small projections were formed which might almost occlude the lumen (fig. 1). These formations might be mistaken for hyaline thrombi, if their origin was not clearly shown in the section. Even then, however, a close inspection showed that the fibrin mass was surrounded by a layer of endothelial cells, separated from the intact vascular endothelium by a space containing red blood cells. Accompanying this deposition of fibrin there was usually some proliferation of the endothelial and subendothelial cells and even of the cells of the rest of the vessel wall and surrounding tissues. Many of these proliferated cells

were of large size and showed basophil cytoplasm, and some were multinucleated (fig. 2). Even when the subendothelial space was full of these cells the normal endothelial lining to the vascular lumen might remain intact.

A similar deposition of fibrin and proliferation of endothelial and subendothelial cells accompanied occasionally by medial changes and a varying degree of periarteritis might be seen in the smaller and some of the larger coronary branches (fig. 3).

As a rule, however, in vessels of a calibre larger than arterioles the picture varied through the occurrence of reactive intimal hypertrophy. In these vessels the earliest reaction was a simple proliferation of the intimal cells

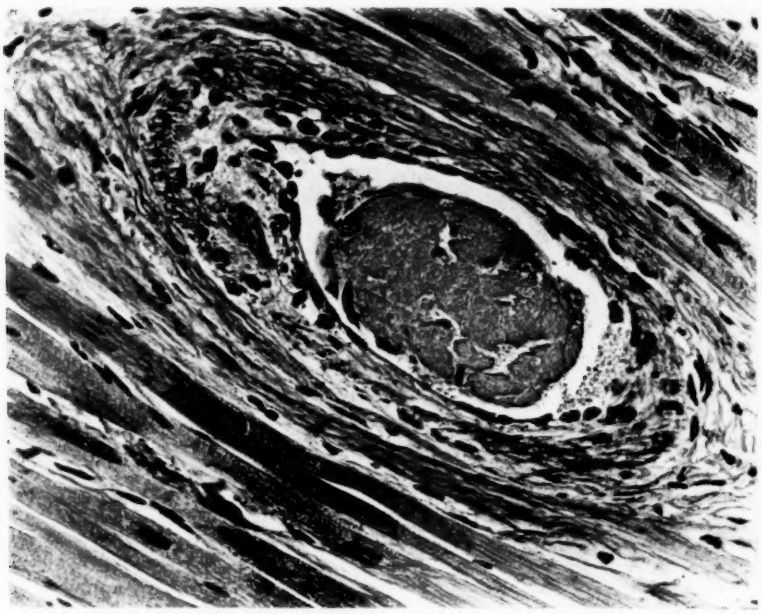

FIG. 1. Case 4.—Arteriole in the inner wall of left ventricle. Note the fibrin and basophil cells in the subendothelial space and the subendothelial exudation of fibrin simulating a hyaline thrombus (× 315).

which might lead to marked intimal fibrosis, or, if the stripe layer became split off from the internal elastic lamina, to the premature formation of those intimal layers which appear with advancing age (fig. 4). Later cellular infiltration and fibrinous exudation occurred in this thickened intima and the intimal cells around the fibrin masses became large and basophil and in some cases multinucleated.

In rare instances these intimal changes were so marked that the lumen became obliterated by the proliferated endothelial cells, fibrin and altered intimal cells (fig. 5).

At other times opposing endothelial surfaces approached one another and finally coalesced so that small portions might become cut off from the main lumen or the whole lumen might become divided up into several small spaces (fig. 6). Sometimes, if there had been much destruction of the internal

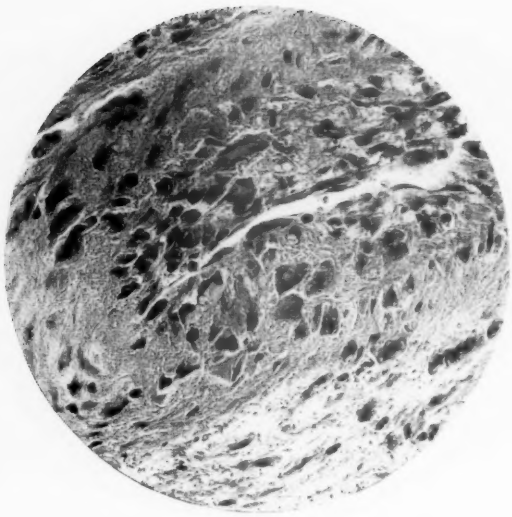

FIG. 2. Case 3.—Small myocardial artery, showing numerous Aschoff cells in the intima (× 315).

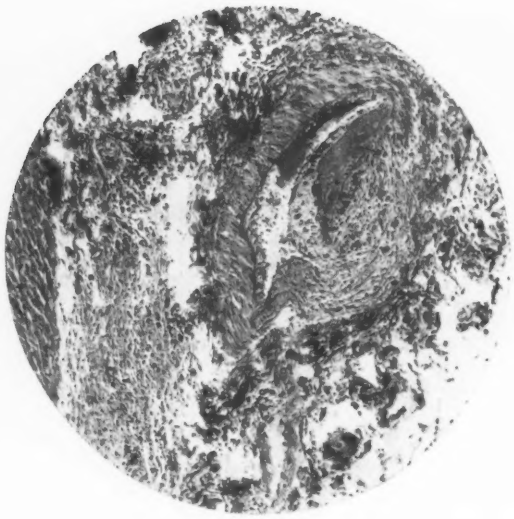

FIG. 3. Case 1.—Artery in the auriculo-ventricular sulcus showing intimal changes. A composite type of Aschoff nodule lies between the vessel wall and the heart muscle (× 90).

FIG. 4. Case 1.—Branch of the anterior descending coronary artery. Note the thick musculo-elastic and elastic hyperplastic intimal layers—the latter showing marked leucocytic infiltration (× 90).

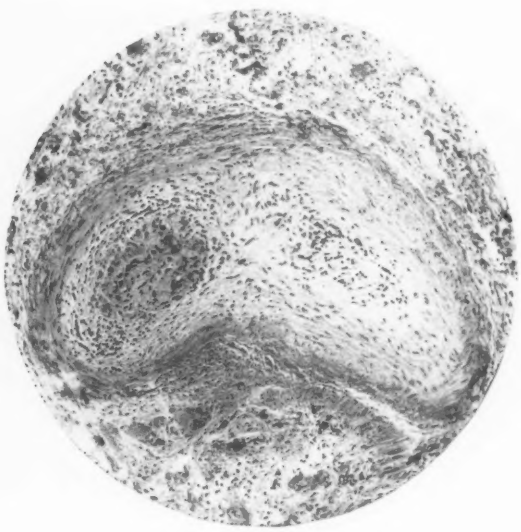

FIG. 5. Case 1.—Branching artery in the auriculo-ventricular sulcus showing occlusion of the lumen. The edge of an Aschoff nodule can be seen in the adventitia at the upper part of the section (× 90).

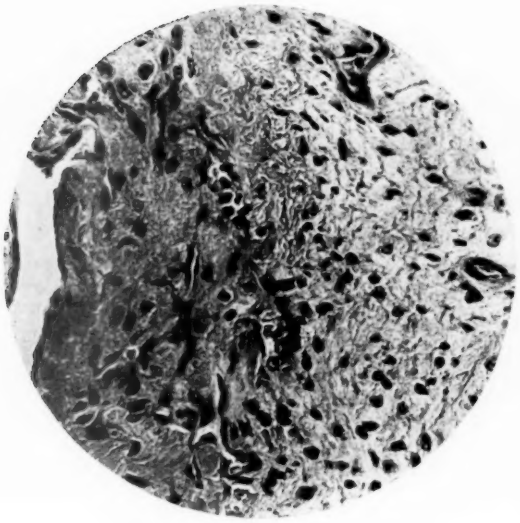

FIG. 6. Case 1.—Intima of a myocardial artery, showing the formation of luminal spaces. The much reduced original lumen is on the left (× 315).

FIG. 7. Case 1.—Artery in the auriculo-ventricular sulcus, showing division of the lumen into four separate spaces. There is degeneration of the internal elastic lamina and stripe layer and much disintegration of the media (× 315).

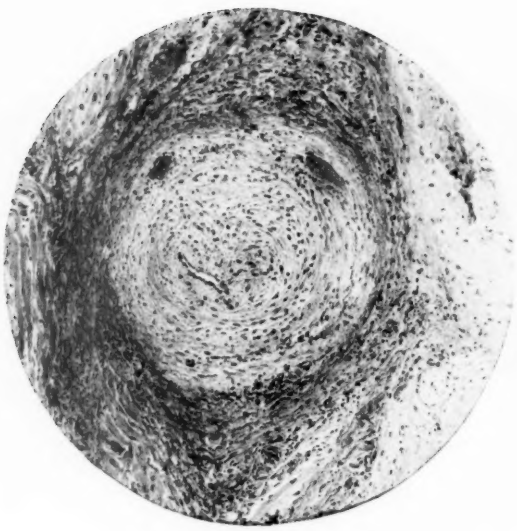

FIG. 8. Case 1.—Artery in the interauricular septum showing hyperplastic intima and two luminal spaces lying within the degenerated internal elastic lamina (× 90).

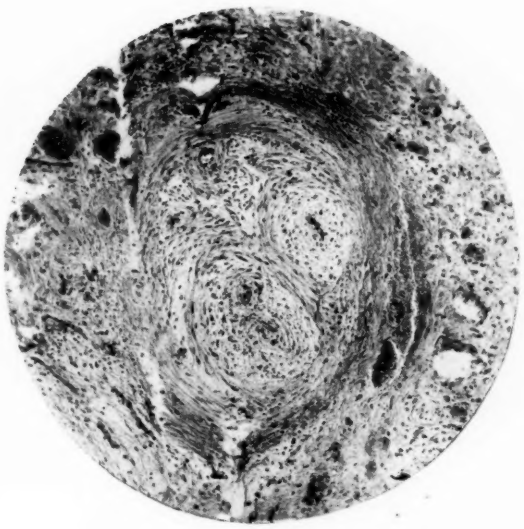

FIG. 9. Case 1.—Artery in the auriculo-ventricular sulcus, showing the formation of muscle and fibrous tissue layers around the luminal spaces (× 90).

elastic lamina and disorganization of the media, a few of these luminal spaces appeared to lie within the media. These blood spaces or luminal rests remained lined by intact endothelial cells which might show basophil cytoplasm, and they communicated both with one another and with the vascular lumen above and below the segment thus affected (fig. 7). There was thus some resemblance to canalization of a thrombus, but thrombosis did not as a rule occur at any stage.

The mobile cells taking part in this intimal inflammatory reaction were chiefly lymphocytes, polymorphonuclears, and plasma cells. Eosinophil cells rarely occurred and then only when the other cells were present in great number.

The internal elastic lamina remained more or less intact, or it appeared as a beaded or segmented ring. Occasionally all that remained of this elastic layer consisted of small scattered portions of degenerated elastic tissue. If the stripe layer of elastic tissue had formed it also underwent similar degenerative changes. The media, even when intimal changes were marked, might remain unaffected. More often there were varying degrees of inflammatory-cell infiltration without much tissue damage. At other times there was marked dissociation of the medial cells and fibres accompanied by much muscle cell atrophy. Occasionally fibrin masses were seen in the affected media, and capillary vessels might also be present. Only very rarely was there any change comparable to coagulation necrosis of the media, and degenerated muscle or other cells with pyknotic nuclei were seldom seen.

The adventitia showed little or no change or it might be involved in the spread of any Aschoff nodules present in the surrounding tissues. More usually there was a diffuse perivascular inflammatory reaction which frequently involved the adventitia, and in such cases there might be some destruction of the external elastic lamina. The cells taking part in this periarteritis were chiefly lymphocytes and polynuclears, but Aschoff cells were frequently seen either singly or as part of a typical nodular area. Often there were numerous capillaries and thin walled blood spaces present and these might communicate with the vessel lumen or what remained of it through capillary channels which passed through the media. A new and accessory circulation was thus established with the collateral blood vessels.

The healing process which followed these inflammatory changes consisted of absorption of the fibrin, disappearance of the mobile and basophil cells and fibrosis. Marked thickening of the intima was produced through the laying down of both collagenous and elastic fibres. The media might become almost entirely replaced by fibrous tissue and there might be marked adventitial and perivascular fibrosis.

The small blood spaces cut off from the vascular lumen sometimes remained and simulated true vascularization of the intima (fig. 8). Occasionally the intimal cells nearest to these luminal rests formed a cuff-like arrangement around them, giving the appearance of somewhat thick walled vessels, in which, so far, it has not been possible to demonstrate the formation

of a new internal elastic lamina (fig. 9). These circularly arranged cells resembled smooth muscle cells in their appearance and staining reactions.

In the later healed stage it might be impossible to differentiate such an affected segment of an artery from a healed and canalized thrombus, except by observing the more acute stages of the intimal lesion at other neighbouring parts of the same vessel or the recrudescence of the acute inflammatory process in the healed segment itself.

Definite evidence of damage to the myocardium as a result of these vessel changes was noticed only in case 1, in which a few microscopical anaemic infarcts were observed here and there along the base of the left ventricle.

Summary and conclusions.

Four cases of acute rheumatism have been described, in which the condition found in the coronary arteries illustrates the occurrence of an endarteritis which is specific in type, the intima undergoing a diffuse inflammatory reaction which reduplicates the histological features of the Aschoff nodule.

The initial change is an intimal cell proliferation which may lead to fibrotic thickening or simple intimal hypertrophy. This is followed by fibrinous exudation or necrosis, mobile cell infiltration, and the appearance of those basophil giant and multinucleated cells which denote the presence of the virus of acute rheumatism. Usually there is marked degeneration of the internal elastic lamina and of any other elastic layers which may have formed in the intima.

Unless complete obliteration of the lumen occurs the vascular endothelium remains intact and thrombosis does not take place. An interesting feature is the occasional isolation of small luminal spaces or even the complete partition of the lumen, which in the later stages leads to the simulation of intimal vascularization or thrombus canalization. Sometimes the intimal cells, in keeping with their mesenchymal origin, reproduce layers of what appear to be smooth muscle cells around these luminal spaces, thus giving them the appearance of thick-walled vessels.

A common accompaniment of this endarteritis is a perivascular inflammation which may be of the Aschoff nodule type or consist of a more diffuse inflammatory reaction with numerous mobile cells, isolated Aschoff cells and many distended blood vessels. Communication between the lumen of the affected segment of the vessel and these perivascular blood vessels is established through the formation of new capillary channels which pass through the media.

The media may remain unchanged or it may be involved through spread of the infection either from the intimal or adventitial side or from both. As a result medial muscle cells disappear and are replaced by fibrous tissue.

Both coronary arteries may be affected and at any part of their course, but the condition is more commonly found in the smaller branches of the left coronary artery.

The vascular lesions observed in these cases show that in acute rheumatism the coronary arteries may be infected not only from the outside, the virus gaining access by way of the perivascular lymphatics, but also from the inside, the virus passing directly into the wall from the lumen.

I have to thank my colleagues on the staff of the Bristol Royal Infirmary for their kindness in allowing me access to the clinical notes of their cases.

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GOUT AND ALEUKAEMIC LEUKAEMIA IN A BOY AGED FIVE

BY

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The case we are about to describe is that of a small boy who, for a period of seven months suffered from a severe anaemia, glandular enlargement and symmetrical multiple arthritis. At post mortem there were found extensive gouty deposits in the joints and subcutaneous tissues, and microscopical examination of the organs showed leukaemic infiltrations of the kidneys and liver.

Case record.

John T., aged three-and-a-half years at the onset of his illness, was quite well until June, 1933. He then gradually became listless and lost weight. He became easily tired and tended to fall rather frequently. During July the parents noticed a swelling under his chin and he came under the care of Dr. Macvie, of Elland. Dr. Macvie found extensive enlargement of the cervical glands and noticed that the child was anaemic. Blood films were taken and the pathologist's report (Dr. Denton Guest, of Huddersfield) on these films was as follows:—'Neutrophil polymorphs 43 per cent.; lymphocytes 51 per cent.; eosinophils 1 per cent.; basophils 2 per cent.; transitional cells 3 per cent. Many of the lymphocytes are of immature type and do not stain well.'

He was treated for a possible tuberculous infection and there was some improvement. He was able to keep about until October 13, when he complained of pain in the ankles which prevented further walking. It was noticed that both ankles were swollen. About this time his stools became frequent and were pale and frothy, and the possibility of coeliac disease was considered. His urine became 'thick like milk,' this being due to an intense phosphaturia. During the following weeks other joints became involved and all were intensely painful. He was seen by one of us on November 26, 1933, and the following day he was admitted to the Leeds General Infirmary.

CONDITION ON NOVEMBER 27:—The child was wasted, fretful and ill. Weight, 28 lb. There was an intense anaemia. His ankles, knees, wrists, elbows and the small joints of his hands and feet were swollen and extremely painful when passively moved (fig. 1). The tip of the spleen was palpable and the liver was enlarged two finger-breadths. His general appearance suggested a severe case of Still's disease, although it was noted at the time that the pain was rather more intense and the anaemia more pronounced than that found in the acute rheumatoid arthritis of childhood.

Examination of the heart showed numerous haemic bruits. The urine by the usual ward tests was normal and clear. The tuberculin tests and Wassermann

reaction were negative. The report of the examination of the blood was as follows:—Red cells 1,040,000 per c.mm.; haemoglobin 26 per cent.; leucocytes 2,950 per c.mm.; colour index 1·3. The red cells stained well and showed some irregularity in size, many of them being definitely larger than normal. There were no nucleated reds. Differential leucocyte count:—neutrophil polymorphs 60·5 per cent.; lymphocytes 36·0 per cent.; monocytes 3·5 per cent.

X-ray examination of the joints and limbs showed nothing unusual apart from the increased shadowing about the joints consistent with a chronic inflammatory condition with much periarticular thickening.

An attempt was made to improve his condition by the treatment of the anaemia with liver extract, and he was given small doses of guaiacol carbonate with iodide of potassium and syrup glycerophos. co. Avoleum. ♏ v, twice daily, was also given. During the following weeks the degree of pain in the joints and also the amount of swelling was much less, and a further blood-count on December 11 gave the following result:—Red cells 2,050,000 per c.mm.; haemoglobin 34 per cent.; leucocytes 8,350 per c.mm.; colour index 0·8. The red cells showed irregularity in size and staining and there were occasional megalocytes. Halometer reading, 6·9. The differential count showed nothing unusual.

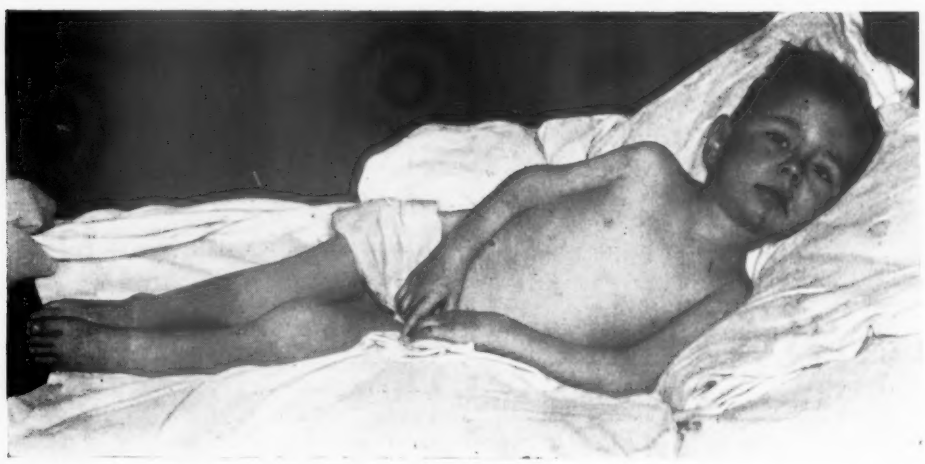

FIG. 1.—The patient on admission to the Leeds General Infirmary.

A third count undertaken a fortnight later showed almost identical figures, but there was now a notable irregularity in the size and shape of the red cells and there was a well-marked megalocytosis. Punctate basophilia was very frequent and nucleated red cells, both normoblasts and megaloblasts, were seen in considerable numbers. As compared with the first examinations it would seem that there was now a good deal of increased marrow activity.

During the last few weeks of the illness there was noticed about the elbows, wrists and knees multiple subcutaneous nodules, which were looked upon as similar to those associated with the rheumatic state of childhood (fig. 2). It was realised at the time that such nodules are not usually found apart from the true rheumatic affections of childhood, but it was thought that their presence supported the belief that the child was suffering from a streptococcal infection of the rheumatic group. Towards the end the liver became greatly enlarged and the spleen was just palpable. There was an irregular pyrexia during the first and last four of the nine weeks he was in the Infirmary. During the whole time he was under observation there was a very obvious generalized glandular enlargement, more especially in the cervical regions and the axillae. His illness terminated with laryngeal obstruction due to oedema following suppuration in the left sterno-clavicular joint, and he died seven-and-a-half months from the onset of his illness.

FAMILY HISTORY. The boy's paternal great-grandmother suffered from gout for many years. The gouty transmission appears to have been passed to the child through his father from two sources, as in addition to the transmission from the great-grandmother her husband's brother also suffered from gout. The only other history of note is that in connection with the child's maternal uncle who died in mid-life from pernicious anaemia.

The post-mortem examination was made 9 hours after death by Professor M. J. Stewart.

EXTERNAL APPEARANCES. The body was emaciated and the abdomen was relatively enlarged. Over both knees and elbows there were numerous small subcutaneous shotty nodules which proved on section to be white chalky deposits of various sizes up to half-an-inch in diameter. Similar deposits were present in the periarticular tissues. The wrists, metacarpo-phalangeal and first inter-phalangeal joints were similarly affected, while round the ankles were present large chalky masses over both

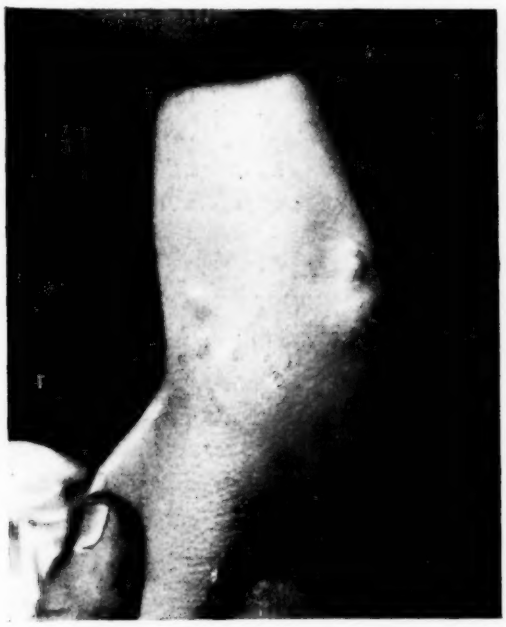

FIG. 2.—Nodules on the elbow.

internal and external malleoli, and the extensor tendon sheaths were covered in front by a flattened mass of the same chalky material. The fingers and toes showed numerous tophi.

JOINTS. The elbow joints showed advanced lesions of a remarkable kind. The interior of the joint, except the actual articular surface, was lined by a thick dead-white layer of dried, friable material more closely resembling white lead than anything else. The ankle joints were equally severely affected, as were the small joints of the hands and feet. The shoulder and knee joints showed what appeared to be an earlier stage of the same lesion, their capsules being lined by an incomplete layer of the same material. They also contained much tenacious glairy fluid, while the elbow and ankle joints were quite dry. The hip joints were free from gouty deposition. The left sterno-clavicular joint was slightly affected, the right not at all. There was no evidence of involvement of the spinal articulations.

KIDNEYS. These appeared slightly enlarged, weighing $4\frac{1}{2}$ oz. The capsules striped readily exposing a smooth surface dotted with white and yellowish-white streaks and patches. On section the organs were pale with very indistinct markings, so that

it was difficult to differentiate cortex and medulla with any certainty. The greater part of the cut surface of both organs showed radial white and yellowish-white streaks affecting mainly the medullary pyramids, though present in cortex as well.

SPLEEN. Weight, 2½ oz. Some areas of congestion were present on section.

LIVER. Weight, 27 oz. This was pale-yellow and fatty-looking.

LARYNX. There was a notable oedema of the glottis, especially of the ary-epiglottic folds.

LUNGS. Some superficial collapse was found.

The other organs, including brain, showed no abnormal findings.

Microscopic examination.—KIDNEY. Scattered throughout the kidney substance, both in cortex and in medulla, were extensive leukaemic infiltrations. These infiltrations were practically confluent in the cortex, where only occasional groups of tubules had escaped. The infiltrating cells had the morphology and staining reactions of ordinary lymphocytes, with small spherical hyperchromatic nuclei, round

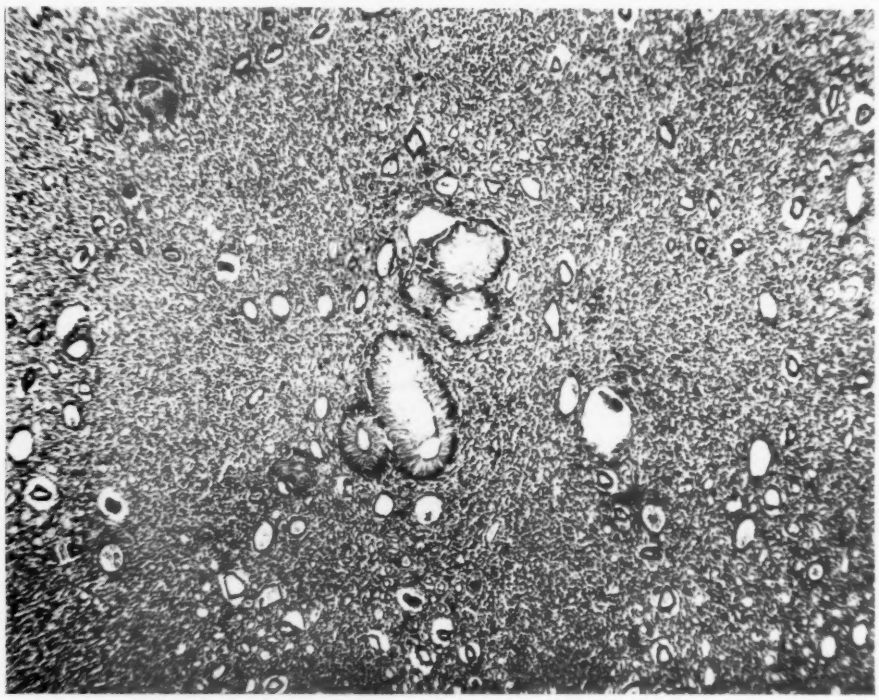

FIG. 3.—Kidney. Four gouty deposits in the medulla. The interstitial tissues are infiltrated by lymphocytes. Low power.

which a little cytoplasm could occasionally be distinguished. In the denser parts of the infiltrations no renal tissue could be identified; elsewhere the renal elements were widely separated and apparently unaffected by the cellular infiltrations. The glomeruli appeared normal apart from some dilatation of the glomeruli spaces; the secretory tubules showed moderately severe degenerative changes, with here and there loss and sometimes absence of nuclear staining and fusion and granularity of cytoplasm. In the medulla the leukaemic infiltrations were not so marked, probably because the larger proportion of connective tissue normally present in the medulla limits its distensibility. The gouty deposits were present in both cortex and medulla though rather more frequent in the latter. They appeared in paraffin sections as circular or oval areas all more or less of similar size, surrounded by a continuous zone of endothelioid cells at right angles to the circumference, with

cellular processes radiating into the mass like the conventional representation of the sun (fig. 3). In a fair percentage of these, giant cells of the usual foreign body type lay at the periphery replacing a group of these endothelioid cells (fig. 4). More rarely a smaller gouty focus can be seen engulfed by a larger giant cell. The uratic material had been dissolved out in the watery fixative (1 per cent. formalin saline) used, but the long processes of the endothelioid cells projecting into the centre of the mass indicated by the spaces between them that the material had an acicular crystalline structure. In the centre of many of the deposits, especially the larger, there were circular or oval thin empty rings of haematoxylin stained granular material, indicating that a small percentage of calcium salts were contained in the uratic material. In others an eosinophilic protein exudate occupied the whole site of the gouty deposit. These deposits were all much larger than the urinary tubules, and it is difficult to say whether they originated in tubules as in the

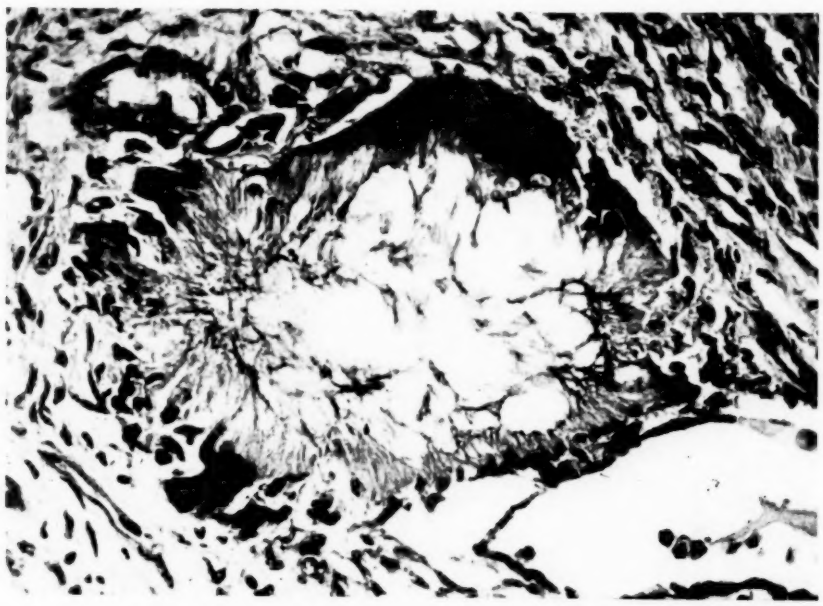

FIG. 4.—Kidney. A high power view of a gouty deposit, showing the endothelioid and foreign body giant cell reaction.

uric-acid infarcts of infants, or in the interstitial tissues as in true gout; but the fact that they were mainly white in the naked-eye specimen strongly suggests that they had an extra-tubular origin, as the uric-acid infarcts of children are formed in the tubules and are coloured yellowish by the urinary pigments. In one or two cases the deposits could be seen protruding into a dilated tubule, but this is most probably the result of mechanical penetration from the increasing size of the deposits. In all cases the reaction to the presence of the gout consisted of endothelioid cells and giant cells, granulation tissue or fully formed fibrous tissue being nowhere in evidence.

LIVER. Here the leukaemic infiltrations were of the same cellular nature as those in the kidney, but they were confined to the dilated portal tracts and the portions of the lobules immediately surrounding them, every portal tract being affected and roughly one-quarter of the total liver substance being composed of the leukaemic infiltrations. These stopped abruptly at the peripheral zones of the lobules, and the parenchymatous tissue was not appreciably invaded. The liver cells showed a moderate degree of fatty change, mainly in the peripheral zones; and

the sinusoids were distended, especially in the centre of the lobules, but contained little blood and no excess of lymphocytes. The Kupfer cells were not unduly prominent.

SPLEEN. There were no leukaemic infiltrations as such in the spleen, but here and there in the pulp were small focal accumulations of lymphocytes, with occasional plasma cells. Macrophages were scanty; there was no excess of haemosiderin. The Malpighian bodies were small for a child of this age, being without germinal centres and sparse in cells.

The other internal organs gave no histological findings of note.

JOINTS. As in the kidney, the gouty material had dissolved in the watery fixative employed; its site is indicated by the haematoxylin staining of the calcium salts or by the protein material that accompanied it. It had often caused practically no reaction when lying free in the joint cavity; it could be removed by hand or washed away in a stream of running water, leaving a smooth and glistening synovial membrane behind. At the edges of the joints and in the tendon sheaths a well-

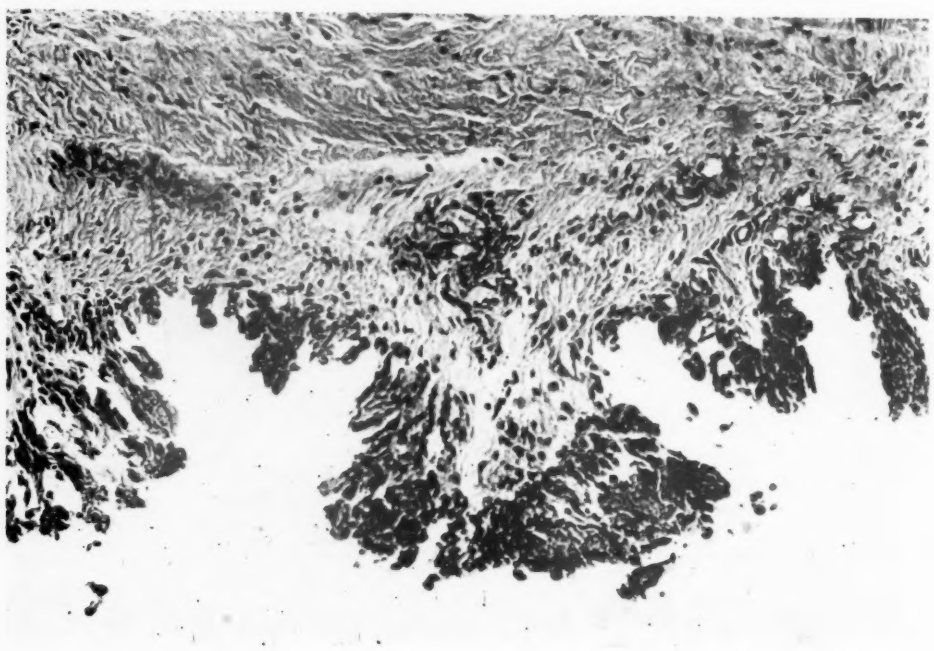

FIG. 5.—Synovial membrane of elbow joint. It is lined by a continuous layer of endothelioid cells and foreign body giant cells. Note the superficial nature of the cellular reaction.

marked cellular reaction had been called out, of the same nature as in the kidney. The synovial membrane was covered by a continuous layer of giant cells of foreign body type, with occasional endothelioid cells. This reaction was a very marked one but was strikingly superficial; the only reaction deeper than this single layer being a few foci of lymphocytic infiltration in the connective tissue immediately underneath (fig. 5). The amount of calcium salts in the uratic material showed great variability; it was generally scanty and showed as a diffuse, faint, bluish staining, but more rarely it was bluish-black, almost as dark as ordinary calcification. In those latter areas the cellular reaction was no more pronounced.

SKELETAL MUSCLES. In the microscopic sections of the joints and tendon sheaths, portions of skeletal muscles often appeared and these showed marked atrophic and degenerative changes. The fibres were either much shrunken and filled only a small

part of the sarcolemma sheaths or else were swollen, glossy and homogeneous with partial or complete loss of the transverse striations. These changes were marked in all the sections, including muscles near all the joints of the extremities; but it was difficult to assess how much of this was due to disuse atrophy and how much was due to the proximity of the gouty deposits, as control pieces of muscle away from the joints were not taken for examination.

Chemical examination.—Dr. Fowweather reports that the gouty material (dried) from the knee and ankle joints contained 64·1 per cent. of sodium mono-urate.

Discussion.

From the report given there can be no doubt that we are dealing with a case of true gout and gout of an extensive nature. Gout in children is a rare condition and the only cases we have been able to find without attempting to analyze the literature are five in number. These comprise two in girls aged seven and eight (Garrod[2]), a child aged three-and-a-half (Still[7]), an adult case who had his first attack in the big toe when aged eight (Scudamore[6]), and a similar case aged fifty, whose first attack occurred at the age of eleven (Duckworth[1]). These cases, however, are quite different from our own; they are merely examples of ordinary gout commencing in early life, and not a generalized disease ending fatally after a short duration. We had imagined that this case would be unique, both in the youthfulness of the patient and the extent of the lesions, but we find that von Schopf[5] recently reported a case in an even younger subject, aged five-and-a-half weeks. The case is so similar to our own that it merits a short description.

The infant was the third child of healthy parents, both of whose families were free from a family history of gout. The child vomited after nearly every meal and the mother noticed hard thickening on the backs of its hands when it was three weeks old. These rapidly increased in size, obvious involvement of the joints could be seen, and the gouty deposits increased with rapidity until the death of the infant from bronchopneumonia at the age of six weeks. The post-mortem examination revealed a condition similar to the case just described and von Schopf's photomicrographs might well have been used to illustrate this paper. In discussing his case von Schopf emphasizes the fact that usual 'causes of gout' could be excluded, the child being breast-fed throughout, and that it illustrates the importance of endogenous purines in the aetiology of gout. There were no leukaemic infiltrations in his case, and he inclined to the view that the features of allergy present, eczema, low temperature, hypermotility of the intestine with increased stools and mucus, support the allergic theory of the pathogenesis of gout.

It is extraordinary that a rare case of gout in a child should be complicated by another rare condition, aleukaemic leukaemia. Leukaemia without leucocytosis has been recognized only in recent years and Hyland[3] reports three typical cases similar to our own. Their ages were five, five-and-a-half, and eight-and-a-ahalf, with total leucocyte counts varying from 1,450 to 8,600 per c.mm., the differential counts showing a percentage of lymphocytes from 22 to 96. A severe anaemia was present in all three cases, with a high colour index, and normoblasts were generally present. All three died, an autopsy being performed on two and showing histologically leukaemic infiltrations of lymphatic type in kidneys and liver.

When this case was described by one of us at a meeting of the British Paediatric Association in May, 1934, the diagnosis of aleukaemic leukaemia was questioned by some on the length of the history (seven months), cases of lymphatic leukaemia of such duration being outside their experience. We would only state that two of Hyland's cases were of long duration, one of seven months and the other of fifteen months, the duration dating, as in our case, from the beginning of symptoms. Apart from this the histology of the liver and kidneys puts the matter beyond all doubt.

The occurrence of gout in association with leukaemia has never, so far as we are aware, been reported in a child. Its association with other diseases has, however, been reported on many occasions, and Roberts and Rose Bradford[4] refer to the development of gout in the adult during the course of myelogenous leukaemia. They point out that in leukaemia the amount of uric acid excreted in the urine is greatly increased. In the cases mentioned by them the gout was in existence before the development of the leukaemia, and so far as we have been able to ascertain no case has previously been reported of gout supervening as a clear sequence of a leukaemia. Also it would appear that when the association has been reported the leukaemia has always been of the myelogenous type.

We would suggest that in our case the leukaemic state was the primary condition and occurring, as it did, in a child whose ancestors were gouty, it led to the precipitation of an acute generalized deposit of urates. Uratosis is seen only in gout and is, indeed, pathogmonic of gout. The association of uric acid with nuclein is clear, uric acid being an oxypurin. The decomposition of nuclein in the body leads to the formation of xanthins and hypoxanthins and these are in part oxidised in the body to uric acid and excreted as such. The explanation seems to be obvious that in the leukaemic state there is available large amounts of nuclein from the breakdown of immature white cells, and when leukaemia arises in the subject carrying the latent tendency to gout the development of uratosis is not unlikely.

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THE SEDIMENTATION RATE IN RHEUMATIC CARDITIS

BY

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One of the difficulties in the treatment of children with rheumatic carditis is the problem of knowing when the activity of the infection in any given attack has come to an end and it is safe to allow the child to return to an active life. Some time ago the leucocyte count in cases of rheumatic carditis was studied in the hope of finding some guide as to the quiescence or activity of the infection from the blood picture. It was found that while there was a definite leucocytosis associated with the disease the change was not sufficiently marked to be of value in assessing activity. Since the original observation by Fåhraeus in 1917 on the sedimentation rate of the red blood cells much attention has been paid to this phenomenon as an index of activity of infection in various acute and chronic diseases. Kahlmeter[6] at the Bath Conference in 1928 was one of the first to draw attention to the value of the sedimentation rate in acute rheumatism, and he described cases in which the raised sedimentation rate did not fall to normal until one year after the onset of arthritis. Ernstene[3] stressed the importance of correcting the sedimentation rate for the degree of anaemia present since a diminution in the total number of red cells, in itself, leads to an increased sedimentation rate. More recently, Åkerrén[1], Payne[7], Bach and Gray Hill[2], and Struthers and Bacal[9] have shown how closely the sedimentation rate parallels the clinical course of rheumatic carditis in children. These observers formed the opinion that the sedimentation rate was the most delicate index of activity of infection in rheumatic carditis, and that it would prove of value in determining the presence or absence of such activity in doubtful cases. Peterman and Seeger[8], however, studied the sedimentation rate in a large number of children and found that so great were the variations met with both in health and ill-health that a single determination was of little value in diagnosis and of no value in prognosis. They found that a single normal or slightly altered rate meant little, whereas a single rapid rate must be held to indicate some abnormality.

It is unfortunate that so many methods of performing this test have been described, the result of which is that it is difficult to compare the results of different workers. One of the difficulties in applying the test repeatedly in children, as is necessary in studying the changes during the course of such a disease as rheumatism, is the fact that the majority of the methods necessitate venous puncture. Payne[7] described a method which

required 0·4 c.c. of blood and stated that he experienced little difficulty in obtaining this from one stab of the finger pulp. In less experienced hands it has proved difficult to obtain this quantity of blood from a finger prick, especially in the case of younger children. The method adopted in this study has therefore been slightly modified from that described by Payne.

Present method.

Into a 0·2 c.c. pipette, 0·03 c.c. of isotonic sodium citrate solution is drawn. A finger is cleaned with spirit, congested with a bandage and pricked. Blood is drawn into the pipette until 0·12 c.c. of blood is obtained (making 0·15 c.c. of blood and citrate solution). This is ejected into a small glass bottle and well shaken. Capillary tubing of 0·5 mm. bore is used as a sedimentation tube. From one end of the tube 10 cm. are measured off and the tube filled with blood to this mark. The bottom end of the tube is then sealed with plasticene and the tube stood upright in a lump of plasticene. The level to which the red cells have sunk is read at the end of one hour. It is found that for clinical purposes this gives all the information required. Since it is rare for the anaemia of acute rheumatism to show any very marked decrease in the number of red cells it has not been considered necessary to correct the sedimentation rate as recommended by Ernstene.

An objection to the use of such a small bore capillary tubing is that if the sedimentation rate is rapid the boundary zone between the clear supernatant plasma and the sedimented red cells is in some cases blurred. This only occurs in the minority of cases and only in those in which the rate is rapid where accuracy of reading to 2 or 3 mm. is not essential.

Results.

In this study 1,043 estimations of the sedimentation rate have been made on 167 children suffering from rheumatic heart disease. The cases have been divided into five groups. The first group comprises 63 children in whom there was no clinical evidence of active rheumatic infection at the time of examination and there was no loss of weight or increase in physical signs when next seen. On these children 202 observations were made. Only one isolated estimation was made in 22 cases and in all of these the sedimentation rate was under 10 mm. in the first hour. The remaining 41 cases had several estimations made in each case (180 in all) over varying periods of time, the average length of time being about eight months. In 3 cases a sedimentation rate over 20 mm. in the first hour was found, in 2 of these it was associated with fever and a ' cold,' but in one case no cause could be found for the abnormal rate. There were also 27 readings over 10 mm. in the first hour; one of these was a child suffering from a ' cold ' and eleven occurred in the same boy who was doing well, gaining weight, with no other evidence of activity, and with no change in physical signs either at the time or later; in the remaining 15 readings no cause for the abnormal rate could be found. Thus over 85 per cent. of the observations made on the sedimentation rate in apparently quiescent cases of rheumatic carditis were under 10 mm. in the first hour. It might be claimed that some of the abnormal rates not otherwise explained might indicate a mild relapse of rheumatism or an observation made at the end of a relapse. In view of the subsequent progress of the case this is unlikely. Since so many factors are known to produce an increase in the sedimentation

rate it is hardly surprising that nearly 18 per cent. of apparently quiescent cases showed abnormal rates, and it must be recognized that a high sedimentation rate in a child with rheumatic heart disease does not necessarily indicate active infection, although, as will be shown later, it should lead to a very careful investigation of the case to exclude such activity.

The cases manifesting evidence of active rheumatism at some time or other during the period of observation have been divided into four groups. The first group is composed of those cases showing chorea as the only sign of rheumatism and with no carditis; the second group consists of those children who had chorea with carditis. In the third and largest group have been considered those cases observed in attacks or relapses of carditis, without chorea as an initial feature, in whom the attack ran a ' monocyclic ' form (Homer Swift). The fourth group comprises the children exhibiting polycyclic types of relapses or attacks.

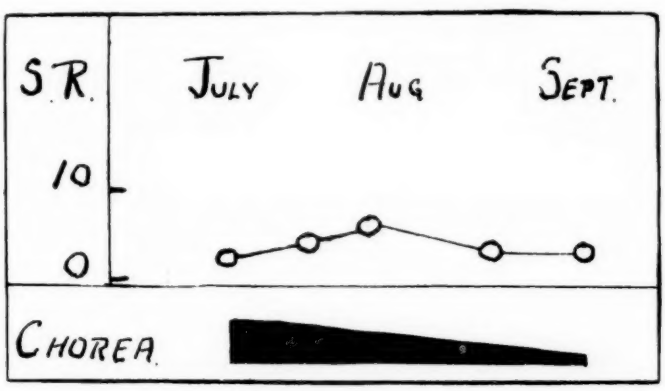

Fig. 1. Case 1.

Thirteen children fell into the first group and on these cases 36 observations were made. All these children had active chorea at the time of the first observation with no evidence of carditis. In one of these the sedimentation rate was 26 at the first observation and gradually fell to 8 in two months. One other case showed a rate of 12 at the first observation which fell to 1·5 in four weeks. With these exceptions the remaining 11 children showed normal sedimentation rates throughout the period of observation. This finding of a normal sedimentation rate in uncomplicated chorea agrees with the observations of Warner[10], Struthers and Bacal[9], and and Faxen[4]. The cause for this is not clear since on all other grounds it is generally agreed that chorea is an active rheumatic manifestation. The following case is typical of the group:—

Case 1.—A girl, aged 13½, had a previous attack of chorea 18 months ago. July 11, 1933: recurrence of chorea; no abnormal cardiac physical signs. July 17: admitted to hospital; chorea steadily improved and was almost recovered on discharge to convalescent home on September 12. No signs of carditis ever detected (fig. 1).

In the group of cases of chorea with carditis a different state of things is found. This group comprised 16 cases and on these 87 observations were made. Two cases of chorea with apparently active carditis showed sedimentation rates under 10, but apart from this all cases had sedimentation rates over 10 and with three exceptions over 20. One case is of interest in that the child was first seen with chorea but with no signs of carditis, the sedimentation rate was 5. When seen later definite signs of carditis were present and the sedimentation rate was now 16, during convalescence it fell again to 5. The highest sedimentation rate observed was 46. Thus in the majority of cases of chorea with carditis a high sedimentation rate is shown in contrast to uncomplicated chorea. The following case illustrates these features:—

Case 2.—A girl, aged 12½, with an old cardiac lesion dating from an attack of chorea at the age of 9 11/12. August 22: quiescent, sedimentation rate 4. November 10: mild chorea, no increase in cardiac physical signs, sedimentation rate 21. November 24: chorea improved, sedimentation rate 13. December 8: no obvious chorea, heart unchanged, sedimentation rate 7. December 29: better, sedimentation rate 4. January 19: going on well, sedimentation rate 8. January 29: sedimentation rate 5. February 12: sedimentation rate 2. March 1: sedimentation rate 2, steady improvement (fig. 2).

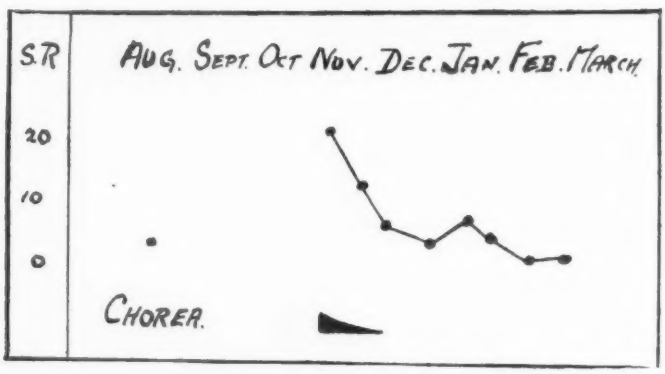

FIG. 2. Case 2.

The third group of cases observed in an acute monocyclic attack or relapse comprised 47 children observed in 49 attacks and on whom 235 observations were made. In this group every case in the attack showed a sedimentation rate over 20. The fastest rate noted in the attack was 60 and the lowest 21. The time taken for the sedimentation rate to return to normal varied from one month to four mouths. Some cases were only seen late in the attack when improvement was obvious, twelve of these showed sedimentation rates under 20 and in 2 cases not seen till 5 or 6 weeks after the attack the sedimentation rate was normal (i.e. under 10). It is interesting to note that two cases during convalescence and after the sedimentation rates had fallen to normal limits developed mild chorea which produced no effect on the sedimentation rate. The following case illustrates this:—

Case 3.—A girl, aged $8\frac{7}{12}$, seen on January 2, 1934, with a history of limb pains last September, not well since, many subcutaneous nodules found on both elbows and on the spines of the vertebrae, slight cardiac enlargement present with a loud apical systolic murmur, sedimentation rate 20 mm. January 9: slight chorea. January 11: marked chorea, cardiac signs unchanged, sedimentation rate 2. January 19: sedimentation rate 2. January 23: chorea persists, no cardiac enlargement, murmur very soft. January 26: sedimentation rate 2·5. February 13: nodules decreasing, cardiac signs unchanged, chorea much less, sedimentation rate 4. February 21: discharged to Torquay (fig. 3).

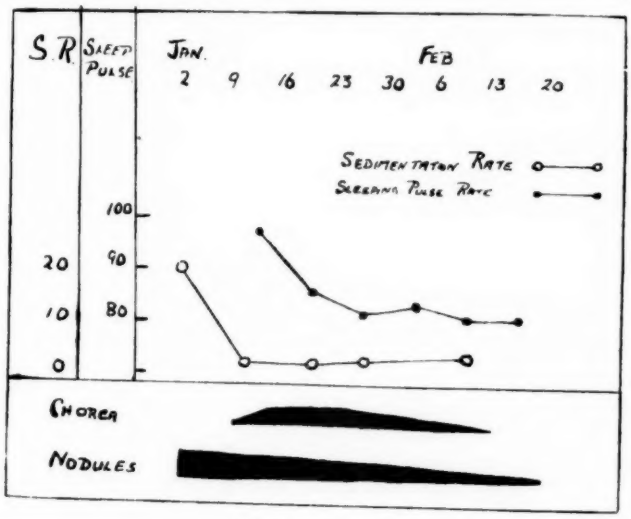

Fig. 3. Case 3.

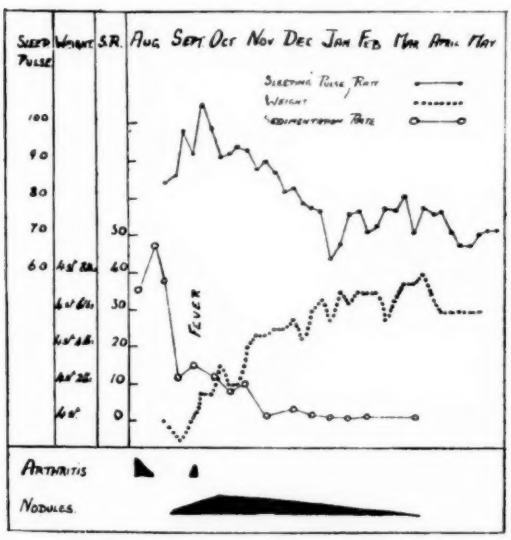

Fig. 4. Case 4.

These cases were observed for varying times throughout convalescence and after recovery from the attack. There were 11 occasions during convalescence when the sedimentation rate was found to be over 10, the highest figure noted being 15 in one case. The following case is typical of the group:—

Case 4.—A boy, aged 10, with an old heart lesion dating from chorea at the age of three. Several relapses had occurred since then. Considerable cardiac enlargement found with systolic and mid-diastolic murmurs at the apex. June and July: going on well, no evidence of activity, sedimentation rate 4 and 3. August 11: one week's history of pains, finger joints red and swollen, sedimentation rate 35. August 15: knees swollen. August 21: sedimentation rate 47. August 31: sedimentation rate 37. September 11: loss of weight, otherwise improved, small nodules over metacarpo-phalangeal joints, knees and ankles, sedimentation rate 13. September 25: nodules larger, cardiac signs not appreciably changed, sedimentation rate 15. September 27: pain and swelling of finger joints lasting two days. October 9: nodules on occiput and spine in addition to others, sedimentation rate 12. October 23: better, nodules unchanged, sedimentation rate 9. November 6: general condition improved, nodules persist, sedimentation rate 10. November 24: improving, nodules unchanged, sedimentation rate 2. December 19: general condition improved, sedimentation rate 4. January 1: nodules smaller and fewer, sedimentation rate 2. January 15: nodules decreasing, sedimentation rate 1. January 29: nodules decreasing, improving rapidly, sedimentation rate 1. February 20: nodules decreasing, better, sedimentation rate 2. March 20: no nodules, sedimentation rate 1·5 (fig. 4).

In the fourth group of children observed in attacks or relapses running a polycyclic course are 27 children, with 30 attacks, and on whom 483 observations were made. In no case during activity was the sedimentation rate under 10, the highest rate found being 68, and the lowest 15. In one case the abnormal rate persisted for 14 months. At the end of this time the child was discharged home but had to be re-admitted almost immediately as she developed an obvious relapse with acute polyarthritis shortly after discharge. Apart from the abnormal sedimentation rate the only evidence of activity was a sleeping pulse rate varying between 85 and 95. With further time spent in hospital the sedimentation rate finally fell to within normal limits. Although in most cases the persistently abnormal sedimentation rate gave a clue to the smouldering infection which was not apparent clinically, yet in some the rate fell to below 10 during remissions. This is shown by case 5.

Case 5.—A boy, aged 15, seen on November 11, 1933, with pains in arms and legs and joints, with swelling of the joints. November 17: admitted to hospital, no definitely abnormal cardiac physical signs, fleeting swelling and pain in all joints, marked erythema marginatum over the whole body. December 6: sedimentation rate 5. December 15: sedimentation rate 12. December 24: much improved, erythema persists. December 29: rise of temperature, relapse of joint pains, apical systolic murmur, sedimentation rate 34. January 3, 1934: nodules on flexor tendons of hands, pains better. January 4: sedimentation rate 23. January 11: sedimentation rate 35. January 19: sedimentation rate 9. January 23: fresh rise of temperature with precordial pain and pericardial rub. January 26: sedimentation rate 49. January 31: fresh rise of temperature with joint pains. February 13: nodules still present, no cardiac enlargement, no apical systolic murmur, no joint pains or rash, sedimentation rate 27. March 5: all physical signs disappeared, sedimentation rate 2. March 16: steady improvement, sedimentation rate 2, no further relapse except for occasional erythema. April 30: sedimentation rate 1·5 (fig. 5).

In one of the cases observed through two attacks the sedimentation rate was abnormal over a month before any clinical evidence of a relapse was found. During convalescence and after recovery four of the cases showed transient sedimentation rate over 10 and in one this was over 20, but this was associated with a transient unexplained fever. There was no

associated clinical relapse of rheumatism. In two cases developing congestive cardiac failure under observation the sedimentation rate became normal, although the disease was obviously active, and in one case that recovered the rate became raised again as the oedema cleared. This

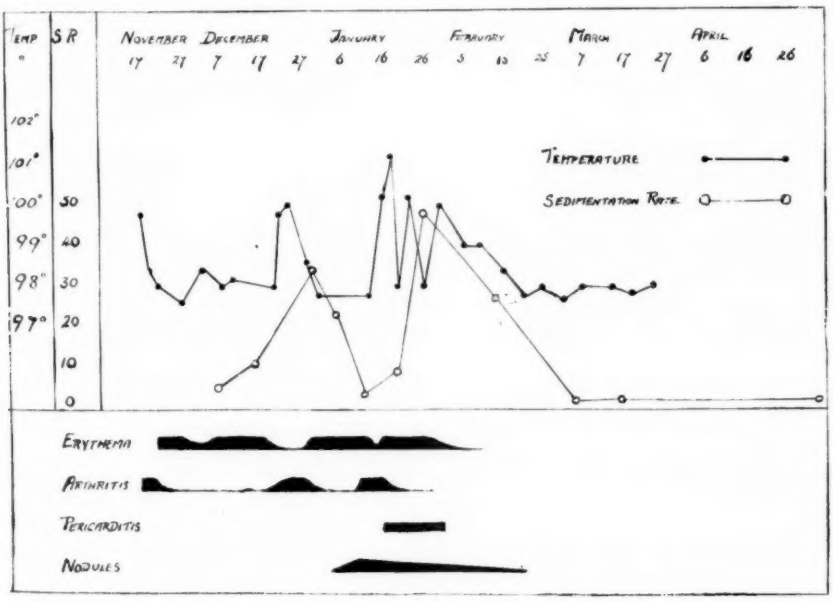

FIG. 5. Case 5.

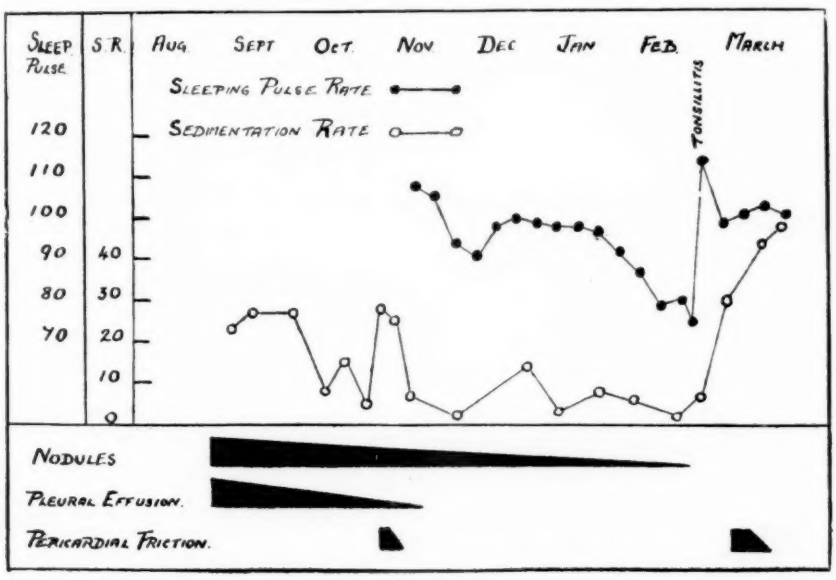

FIG. 6. Case 6.

anomaly is presumably to be explained by a change in the plasma proteins coincident with the oedema, since there is much evidence that these play an important part in regulating the sedimentation rate of the red blood cells. Case 6 illustrates the features of this group.

Case 6.—A girl, aged 13, seen in August, 1933, with an acute relapse of carditis and left sided pleural effusion together with many subcutaneous nodules; sedimentation rate 23. Slow improvement with fall of sedimentation rate to 5 on October 17. October 23: relapse with pericarditis, sedimentation rate 29. Gradual improvement followed, sedimentation rate falling to 7 on November 6. Gradual improvement with fall in sleeping pulse rate and gain in weight, and by February 19 the nodules had practically disappeared. February 21: haemolytic streptococcal tonsillitis. This was followed by rapid loss of weight. March 1: an aortic diastolic murmur noted for the first time; sedimentation rate 30. March 8: pericarditis, friction persisting for more than 10 days. March 15: sedimentation rate 44. March 20: clinically improved, sedimentation rate 49. The child was removed from hospital against advice and died 14 days later (fig. 6).

Discussion.

The high sedimentation rate found in acute rheumatism is in no way a specific reaction since many other infections, both acute and chronic, show a similar change. The absence of any constantly high sedimentation rate in chorea uncomplicated by carditis is puzzling. Payne (personal communication) has suggested that this finding is due to the fact that the cases with chorea have not come under observation until late in the disease when the chorea is a residual phenomenon. The two cases who developed chorea during convalescence from an attack of rheumatism with no change in the sedimentation rate suggest that this is not the true explanation. It was hoped that the sedimentation rate might provide a clue to those smouldering cases which show no gross clinical evidence of activity, but deteriorate rapidly on being set free from restraint and treatment. In some cases this is so and it is clear from this study that any rheumatic child showing a persistently abnormal sedimentation rate should be regarded as having active disease unless some other cause for the blood change can be found. Unfortunately the reverse does not hold true—namely that any single normal sedimentation rate excludes the possibility of a smouldering activity, but if the sedimentation rate is persistently low it is unlikely that the rheumatic process is active. This observation raises an interesting point, whether some of these cases should be regarded as exhibiting exacerbations of a long drawn out infection or rather acute reinfections during convalescence.

Observations on the correlation between the sedimentation rate and the development and duration of subcutaneous rheumatic nodules have also been made. In all, 16 cases had subcutaneous nodules. As is usual the nodules developed at the end or late in the attack and in 9 of the cases they appeared when the sedimentation rates had fallen to between 10 and 20, in 6 the sedimentation rate was over 20 at the time that the nodules first appeared; in the remaining case which was not seen until the nodules had appeared the sedimentation rate was 6. On the other hand, in no case, in which the development of nodules was observed, did fresh nodules appear after the sedimentation rate had fallen below 10. There is one possible exception to this statement and that is case 5. In this instance nodules

developed seven weeks after the first attack of rheumatism but at the height of a relapse and between the two acute phases the sedimentation rate had fallen to normal. Whether the nodules should be related to the initial attack or to the exacerbation, it is difficult to say but they persisted through a further exacerbation, lasting in all just over two months.

Thus these observations confirm previous reports of other workers that an acute attack or relapse of rheumatic carditis is associated with a rapid sedimentation rate of the red blood cells. This abnormality of the blood returns to normal after a variable period of convalescence, and it is clear that no case can be regarded as recovered from the acute phase of the disease in which the sedimentation rate remains high. The sedimentation rate is altered early in the course of the disease and may be abnormal before any clinical signs of a rheumatic relapse are evident. On the other hand, in some cases running a protracted polycyclic course the sedimentation rate may return to normal and yet obvious clinical signs of activity recur within two or three weeks. Whether the sedimentation rate should be regarded as the true index of activity and the apparent exacerbation as actually a fresh infection, is a difficult point to determine, but from the fact that such cases present no clinical differences from those in which the sedimentation rate remains abnormal throughout makes it appear unlikely. At the same time in certain cases the abnormal sedimentation rate may be the only sign of activity of the infection and if such cases are followed up clear evidence of active disease appears.

Conclusions.

(1) Acute rheumatic carditis is always associated with a high sedimentation rate.

(2) Chorea uncomplicated by carditis may show a normal sedimentation rate.

(3) The sedimentation rate is an accurate index of active infection in rheumatic carditis.

(4) While active carditis is unlikely in the presence of a normal sedimentation rate, repeated observations are essential to confirm the absence of infection in cases running a polycyclic course.

(5) Subcutaneous nodules appear late in the course of the disease as judged by the sedimentation rate and may persist after complete quiescence of the disease is established.

(6) With the onset of congestive cardiac failure in acute rheumatic carditis the sedimentation rate returns to normal.

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NEPHRITIS IN INFANCY

BY

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Although the subject of nephritis has been studied from many aspects, comparatively few reports are extant on the manifestations of the disease as it occurs in infancy. In this communication are discussed the cases of nephritis, ten in number; occurring in infants under eighteen months admitted to the Royal Hospital for Sick Children, Glasgow, during the past three years. The cases described constitute 0·4 per cent. of total admissions to the medical wards of the same age period and 5·5 per cent. of all cases of acute nephritis under thirteen years.

Case records.

In addition to the clinical and biochemical findings short notes of the post-mortem manifestations in the fatal cases are given.

Case 1.—J. McD., admitted 18.2.33, was a boy aged nine months, a fourth child, with a good family history. Pregnancy and labour had been normal. He was breast-fed and throve well till a week before admission when oedema, first noticed in the face, appeared. On admission he was found to be a fairly well-nourished child, afebrile, with marked anasarca and ascites present. The Wassermann reaction was negative. The urine contained 20 gm. per litre of albumin, with a positive guaiacum reaction and numerous casts and red blood corpuscles.

The biochemistry of this case is of particular interest because of the fact that nine observations were made on the serum proteins during the course of the disease until recovery was established. As can be seen from the following figures, a close relation exists between the serum oncotic pressure level and the extent of the oedema.

A high protein diet containing 68 gm. protein per day or about 8 gm. per kgm. body weight was given for four weeks. From the time of the first observation calculated serum oncotic pressure rose steadily. When it reached 20·2 mm. Hg. no oedema was observed (see fig. 1). At that point the albumin in the urine had fallen to 1 gm. per litre.

Date	Total prot. gm.	Alb. gm.	Glob. gm.	N.P.N. mgm.	Onc. press mm. Hg. (calc.)	Serum Ca. mgm.	Serum Phos. mgm.	Wt. (Kg.)	Remarks.
	All percentage figures.					Percentage figures.			
19.2.33	3·67	1·80	1·87	28·0	12·5	7·8	4·8	10·5	Oedema + +
27.2.33	4·24	1·80	2·44	27·0	13·3	8·2	4·3	10·7	,, ,,
13.3.33	3·92	2·38	1·54	27·2	15·2	5·5	4·9	10·7	Orchitis, fever
22.3.33	4·34	2·19	2·15	20·0	15·0	6·3	4·7	10·3	,, ,,
24.3.33	6·22	2·16	4·05	25·3	17·5	11·0	4·9	9·5	Oedema less
29.3.33	6·78	2·24	4·54	25·0	18·7	9·0	5·2	8·4	Testicular abscesses
10.4.33	5·83	2·93	2·89	41·6	20·2	8·6	—	8·2	No oedema
13.4.33	5·86	3·54	2·32	37·0	22·7	—	—	—	,, ,,
25.9.33	6·99	4·18	2·81	27·0	26·9	—	4·8	—	,, ,, Urine clear.

* The work was carried out during the tenure of a Carnegie Research Scholarship.

At first glance cure in this case may seem to be connected with the administration of a diet high in protein for which some observers claim good results in the treatment of lipoid nephrosis and the nephrotic syndrome of glomerulo-nephritis. It is, however, well known that spontaneous rise of serum proteins may occur, and in this case after four weeks of high protein feeding the diet was changed to half milk, providing only 2·0 gm. of protein per kgm. body weight, and this did not interfere with the rise of serum proteins (see fig. 1). It is also known that infections may cause a rise in

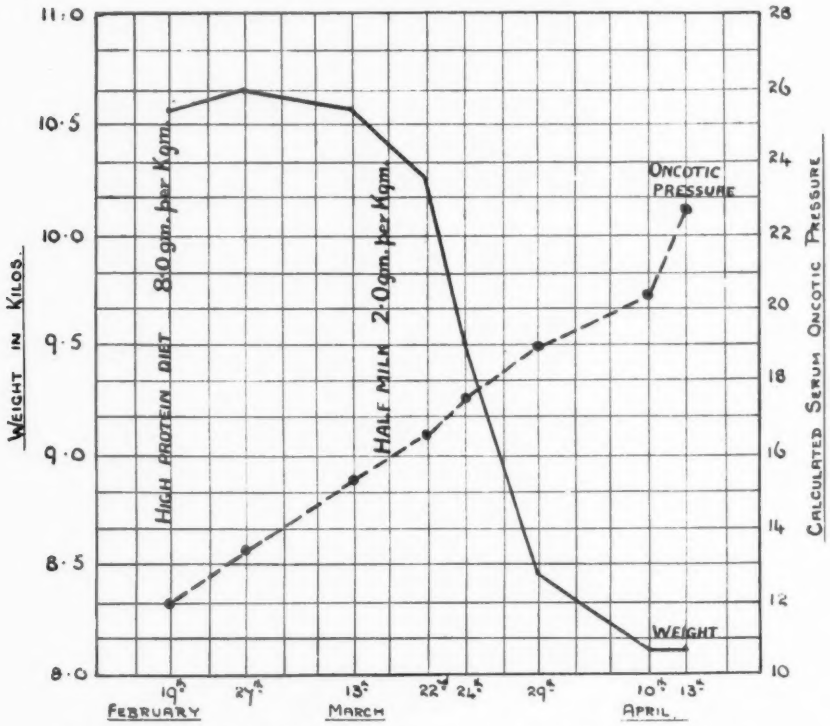

FIG. 1. Relation of oncotic pressure of the serum to oedema.

serum globulin (Bruckman et alii[1]). In this case the development of suppurative orchitis probably accounted for the high globulin found on 24.3.33 and 29.3.33. If the theory of Epstein[2] and others that the nephrotic syndrome is a metabolic upset be correct and that the normal production of serum proteins is interfered with, then it is possible that an infection may act as a stimulus to the production of serum proteins, but the possibility of rise in serum albumin being spontaneous must not be lost sight of as a steady return to normal occurred from the first blood observation. Non-protein nitrogen was normal save on the occasion when it reached 41·6 mgm. per cent. This slight rise above the normal level was possibly associated with the suppurative process. Serum calcium on the whole tended to be low when serum protein was low though this was not invariably the case. Serum phosphorus was normal. That the reduction of serum protein was not due to dilution of the blood may be inferred (a) from the observation

that the protein fractions were not reduced equally and (b) from the fact that the haematocrit readings, the red cell count and the haemoglobin level were normal. No red blood corpuscles were seen in the urine after the eighth day in hospital. Seven months after the onset of the illness the child appeared to be perfectly well, at which time the urine contained no abnormal constituents and serum proteins were normal.

Case 2.—I. G., a female, aged one year and three months, was an only child of healthy parents, breast fed till nine months and throve well. Six weeks before admission both ears discharged pus for four weeks and the child became pale, listless and vomited occasionally. Four weeks before admission a purulent nasal discharge began. There was no history of oedema. Admitted to hospital on 7.9.33, she was a pale child, fairly well nourished, with a puffy face and slight pitting over the tibiae. Nothing abnormal was detected in the heart, lungs, nervous system or abdomen. Ophthalmoscopic examination was negative. The urine contained 3·5 gm. of albumin per litre, red blood cells were exceedingly scanty and some casts were seen. Culture of the urine was negative. Two days later the body weight had remained stationary but slight fever had developed, the temperature reaching 100° F., with the reappearance of a purulent nasal discharge. The Wassermann reaction was negative. The blood pressure in mm. Hg. was 98 systolic and 56 diastolic. Puffiness of the face was still present.

18.9.33. Oedema was absent. Passage of loose green stools commenced on 17.9.33. with frequent vomiting.

21.9.33. The child was removed from hospital against advice. 1·2 kg. body weight had been lost during past four days. Enteritis was still present, but there was no oedema.

14.10.33. The child was seen as an outpatient. Since discharge the enteritis had continued and the baby appeared to be very dehydrated and ill. A catheter specimen of urine showed no albumin, casts or blood. The mother refused to leave the child in hospital and the child died at home five days later. (No examination of the blood was made on 14.10.33).

The following are the blood chemistry findings:—

Date	Total prot. gm.	Alb. gm.	Glob. gm.	Onc. press. mm. Hg. (calc.)	N.P.N. mgm.	Oedema	Remarks
	Percentage figures				per cent.		
9.9.33 ...	3·80	2·40	1·40	15·2	29·2	±	
18.9.33 ...	5·21	2·13	3·08	16·0	28·0	—	Enteritis

It can be seen that rise in serum oncotic pressure was but slight. Even at as low a level as 16·0 mm. Hg. oedema was absent. It is probable that the dehydrating influence of the enteritis played a large part in the disappearance of the oedema. Possibly the rise in serum globulin was associated with the presence of an infection or, less probably, may have indicated spontaneous regeneration of the serum proteins.

Case 3.—A. H., was a boy six months old. The first pregnancy ended in a miscarriage, but otherwise the family history was good and the patient's three brothers and sisters were alive and well. Breast fed for one month he afterwards received Nestlés milk. He throve until at five months old he contracted chicken-pox which was followed a week later by enteritis. Two weeks later generalized oedema was observed and he was admitted to hospital on 16.6.31.

He was a well-nourished infant with oedema involving face, sacrum, scrotum, thighs and legs. Ascites was also present. In the lungs some rhonchi were heard. In the heart and nervous system no abnormality was detected. The urine contained 11 gm. of albumin per litre and the guaiacum reaction was positive. Numerous red blood corpuscles and casts were present. Urine culture was negative; the stools were loose and green. An ophthalmoscopic examination was negative.

16.6.31. Blood pressure was 85/55 mm. Hg.

Blood chemistry.—Total protein 4·09 gm. per cent.; albumin 1·63 gm. per cent.; globulin 2·46 gm. per cent.; calculated serum oncotic pressure 12·4 mm. Hg.; N.P.N. 27·5 mgm. per cent.; and serum Ca. 5·4 mgm. per cent.

From the day of admission enteritis continued and the child steadily lost weight (2·3 kgm.), became dehydrated and died on 24.6.31.

A post-mortem examination showed enteritis and hypostatic congestion of lungs. On histological investigation a mixed type of nephritis was found, the changes being chiefly in the tubules. No evidence of congenital syphilis was found.

Case 4.—S. C., a male aged one year and four months, was the tenth child of healthy parents. Their second child was still-born and the rest of the family history was not relevant. He was breast fed and throve till eleven months old when he developed ? encephalitis and was in the Royal Hospital for Sick Children for six weeks. At that time the Wassermann reaction of blood and cerebrospinal fluid was found to be negative. The urine contained no abnormal constituents. A week before his second admission generalized oedema occurred but no abnormality of the urine was observed by the mother. Re-admitted to the Royal Hospital for Sick Children on 30.8.32, aged one year and four months, he had oedema of face, sacrum and legs. Ascites was also present. The urine contained much albumin, 14 gm. per litre and the guaiacum reaction was positive. Numerous red blood cells and casts were present. The urine culture was negative.

Blood chemistry, 31.8.32.—Total protein 4·54 gm. per cent.; N.P.N. 24·1 mgm. per cent.; and serum Ca. 6·4 mgm. per cent.

During a stay in hospital of 22 weeks oedema was present in varying degree for 16 weeks. It diminished during administration of ammonium chloride and also during a febrile period due to otitis media but also at other times for no apparent reason and the reduction of oedema could not be related to any form of diet or therapeutic measure. Haematuria persisted for 15 weeks. Albuminuria was present throughout and the child was dismissed as a chicken-pox contact while the urine still contained much albumin. Blood was absent.

6.6.33. Child reported in out-patient department much improved. A cough had been present for two weeks. No oedema had been observed: temperature 100° F. Numerous rhonchi were audible in both lungs. Urine contained a trace of albumin but no casts nor red cells were seen. The blood chemistry findings were:—total protein 9·95 gm. per cent.; albumin 5·83 gm. per cent.; globulin 4·12 gm. per cent.; calculated serum oncotic pressure 37·8 mm. Hg.; and N.P.N. 25 mgm. per cent.

6.4.34. Urine normal.

While in this case serum albumin and serum globulin were not estimated separately during the stay in hospital it can be seen that there was a rise of serum proteins to above normal level. This is due to increase in both albumin and globulin, the high globulin being probably explained by the presence of the respiratory infection which later was found to be whooping cough.

Case 5.—C. G., a male, was aged four months. Family history was good. He was breast fed and throve till two weeks before admission when puffiness of the face was noted. Admitted to hospital on 4.2.33, he had oedema of face, sacrum and legs

and some ascites. The heart, lungs and nervous system showed no abnormality. The urine contained much albumin but casts were not numerous and red cells were very scanty. Urine culture was negative.

Blood chemistry, 6.2.33.—Total protein 4·84 gm. per cent.; albumin 1·60 gm. per cent.; globulin 3·24 gm. per cent.; calculated serum oncotic pressure 13·3 mm. Hg.; N.P.N. 50 mgm. per cent.; serum Ca 5·8 mgm. per cent.; serum phosphorus 7·0 mgm. per cent.

12.2.33. Numerous loose stools were passed during the stay in hospital and on 14.2.33 child became comatose and began to have convulsions. Lumbar puncture was performed and the cerebrospinal fluid was found to be normal. Death occurred on the same date.

Post-mortem examination showed marked oedema of the brain. No evidence of congenital syphilis was found. Areas of intense congestion were present in the small bowel. Both kidneys were swollen and the capsule was slightly adherent. Histologically subacute nephritis was present with well-marked tubular involvement and extensive proliferation of the interstitial tissue with foci of round-cell infiltration.

There are two possibilities. (a) The convulsions may have been terminal and due to an intense toxaemia arising from bowel infection. (b) The convulsions may have been symptomatic of true uraemia and it is somewhat significant that the only instance of convulsions in this series occurred in the child whose kidneys showed interstitial changes. This together with the increased concentration of non-protein nitrogen and inorganic phosphorus in the blood lend some support to this view.

Case 6.—G. A., a boy, aged one year and four months, was admitted on 7.9.33. He was a healthy infant, breast fed for one month, then receiving cow's milk till one year old and subsequently a mixed diet. He throve till four weeks before admission when he began to refuse food and two weeks before admission oedema of the face was noted. On admission he was found to be a small child with moderate degree of oedema of the legs, face and sacral region. The blood pressure was 100 mm. Hg. systolic and 70 diastolic. Ophthalmoscopic examination was negative. The urine contained albumin up to 12 gm. per litre but red cells were very scanty although casts were numerous. The Wassermann reaction was negative. Urine culture was negative. As previous experience had shown that fatal enteritis was prone to supervene in such cases this child was dismissed from hospital although the urine still contained albumin, 4 gm. per litre, and there was still slight oedema. On dismissal the child attended the out-patient department and was observed to weather an attack of diarrhoea shortly afterwards. Two weeks following dismissal the urine was found to be quite free of albumin. The oedema had disappeared entirely during the attack of diarrhoea and never returned. Since that time the child has been perfectly well.

Blood chemistry.

Date	Total prot. gm.	Alb. gm.	Glob. gm.	N.P.N. mgm.	Onc. press. mm. Hg. (calc.)	Serum ca. mgm.	Serum phos. mgm.	Wt. (kgm.)	Remarks
	Percentage figures					Percentage figures			
8.9.32	4·51	2·92	1·59	28·5	18·3	9·2	5·5	8·4	Oedema +
14.9.32	5·63	2·25	3·38	35·7	17·1	7·3	4·8	7·7	Oedema ±
15.5.33	7·31	5·32	1·99	31·2	31·8	—	—	—	Oedema gone; urine clear

The diminution in oedema at the time of the second observation (14.9.32) while serum oncotic pressure had fallen slightly may be explained by the fact that while in hospital the child was receiving a diet of milk, containing much less salt than is found in mixed diet. The rise in globulin on 14.9.33 may have been indicative of regeneration of the serum proteins but more probably was a reaction to the bowel infection.

Case 7.—J. N., a male aged one year, was an only child of healthy parents who was breast fed and throve till two weeks before admission when oedema was observed. Admitted to hospital on 26.10.31, the patient was a big child with marked oedema involving face, chest wall, lumbar region and legs. Ascites also was present. The heart, lungs and nervous system showed no abnormality. Ophthalmoscopic examination was negative. Blood pressure was 98 mm. Hg. systolic and 60 diastolic. The urine contained much albumin and the guaiacum test was positive. Casts and red cells were numerous. Urine culture was negative.

BLOOD CHEMISTRY. Total protein 4·23 gm. per cent.; albumin 1·96 gm. per cent.; globulin 2·27 gm. per cent.; calculated serum oncotic pressure 13·9 mm. Hg.; N.P.N. 36·3 mgm. per cent.; serum calcium 9·8 mgm. per cent.; serum phosphorus 5·4 mgm. per cent.

On the day after admission severe enteritis developed, much oedema was lost but some was still present along with much albumin and blood in the urine when the child died six days after admission. Permission for an autopsy was refused. This child died of enteritis complicating nephritis.

Case 8.—E. K., was a female aged seven months, whose family history was good. She was fed on whole cow's milk and progressed well till three weeks before admission when swelling of the face was noticed and a week before admission the abdomen became prominent. Admitted to Royal Hospital for Sick Children on 23.6.31, she was a small child with moderate oedema of feet, slight ascites and puffiness of the face. The urine contained much albumin—11 gm. per litre—scanty casts and red cells. Culture of the urine was negative.

27.6.31. The child died, stools being frequent and vomiting persistent for the preceding four days. No oedema was then apparent, 1·70 kgm. having been lost.

POST-MORTEM EXAMINATION. A few patches of bronchopneumonic consolidation were present in the lungs. No evidence of congenital syphilis was found. Histological report: early acute glomerulo-nephritis with marked cloudy swelling of the tubular epithelium present.

Case 9.—G. R., a male aged eight months, with a good family history, was breast fed and throve till four weeks before admission when generalized oedema was observed. The urine at that time was reported to be dark in colour. Admitted to hospital on 17.10.31, he had a marked degree of oedema involving face, legs and lumbar region. Slight ascites was present. Examination of heart, lungs and nervous system showed no abnormality. The urine contained albumin, 15 gm. per litre, the guaiacum reaction was negative and red cells were scanty. Casts were fairly numerous.

BLOOD CHEMISTRY, 21.10.31. Total protein 6·78 gm. per cent.; albumin 2·66 gm. per cent.; globulin 4·12 gm. per cent.; calculated serum oncotic pressure 20·4 mm. Hg.; N.P.N. 29·1 mgm. per cent.; and serum Ca. 9·2 mgm. per cent.

22.10.31. Oedema much less. Fever, present since day after admission, increased steadily and signs of pneumonia were noted on 23.10.31. The stools became loose and the child lost oedema rapidly and died nine days after admission.

POST-MORTEM EXAMINATION. Both lungs showed bronchopneumonia. The brain was oedematous. No evidence of syphilis was detected. Histological report of kidneys: early acute glomerulo-nephritis was present with well-marked swelling of the convoluted tubules.

This child died of pneumonia complicating acute nephritis. From the high serum oncotic pressure level it is likely that blood examination was carried out after diuresis had begun. This is borne out by the rapid loss of oedema which was observed on the following day. Presumably the pneumonia was responsible for the increase in globulin which compensated for the deficiency in albumin and thus allowed serum oncotic pressure to reach a level compatible with diuresis.

Case 10.—S. L., was a boy aged one year and one month. The first and third pregnancies ended in stillbirths. He was breast-fed and throve till a fortnight before admission when oedema developed and the urine was observed to be dark in colour. Admitted to hospital on 5.4.34 with generalized oedema and ascites. No abnormality was detected in heart or lungs. The urine contained albumin—20 gm. per litre—and much blood. Casts were numerous. The Wassermann reaction was negative. The child was afebrile till the development of a cellulitis of the abdominal wall on 29.4.34 which proved fatal on 1.5.34.

BLOOD CHEMISTRY.

Date.	Total prot. gm.	Alb. gm.	Glob. gm.	Onc. press. mm. Hg. (calc.)	N.P.N. mgm.	Serum Ca mgm.	Serum Phos. mgm.	Weight (kgm.)
	Percentage figures.				Percentage figures.			
6.4.34	4·32	2·46	1·86	16·1	65·2	8·1	6·6	10·5
11.4.34	4·91	2·52	2·39	17·2	39·9	—	—	10·3
1.5.34	4·27	1·39	2·88	11·7	29·1	4·7	—	10·8

In this case some nitrogen retention was present on the first blood examination but not subsequently. Permission for autopsy was refused.

Previous work.

Before the clinical features and biochemical findings of the present series are discussed it is proposed to summarize the published reports of previous investigations. As has already been said the literature on nephritis in the period of infancy is scanty.

Henoch[3] recognized the existence of both acute and chronic nephritis in infants and noted that oedema was its most prominent manifestation. In the edition of his text-book published in 1899, Holt[4] described the symptomatology of what he termed acute exudative nephritis in children under two years but included as synonymous titles acute desquamative nephritis, acute parenchymatous nephritis and acute septic interstitial nephritis. In the condition he described, the onset was abrupt with high fever and vomiting, while oedema was exceptional, being present in only six out of twenty-three cases and then slight in degree and only towards the termination of the disease. Dyspnoea was observed frequently but was ascribed to anaemia. Muscular twitchings were common and convulsions occurred in three cases. Albuminuria, frequently absent early in the attack, was rarely gross. Although casts were not usually numerous, many pus and endothelial cells were seen together with red blood corpuscles in moderate numbers. The mortality was high. At autopsy the kidneys presented a mottled appearance due to the aggregation of pus cells and even abscesses were often found. It seems evident that Holt was describing pyelonephritis, and in later editions of his book he did not include these symptoms in his descriptions of acute parenchymatous nephritis.

Spence[5], also states that oedema is rare and emphasizes the presence of marked dyspnoea which he attributes to nephritic acidosis. He considers azotaemia an important diagnostic feature, the level of the non-protein nitrogen in the blood occasionally being as high as 100-150 mgm. per cent. He states that the prognosis is grave. Such a description might include any condition associated with severe toxaemia and dehydration, since albuminuria, acidosis and azotaemia are not uncommon features in these conditions. But against this objection Spence[5] mentions the presence of casts and blood cells in the urine.

A series of cases reported by Boyd[6] were hydraemic in type and resulted in almost 100 per cent. cure unless fatal secondary infection occurred. Still[7] mentions the occurrence of uephritis with oedema in an infant five days old. In forty-nine cases of acute nephritis in children, Paterson and Wyllie[8] record seven of parenchymatous type occurring between the age of one and three years. Of the series reported by Lyttle and Rosenberg[9], of seventy-four cases of acute glomerular nephritis, seventeen acute diffuse and eight acute tubular, three, one, and two cases respectively occurred under two years. Levy[10] found seventeen cases of nephritis in infants under a year in 1,000 admissions to hospital over a period of ten years. Of these seventeen, fourteen died, giving a mortality rate of 82 per cent. as against one of 19 per cent. for total admissions. These cases he divides into three groups of different aetiology: (a) Nephritis complicating erythrodermia desquamativa—five cases. All these patients died, four of the primary disease and one of sepsis. (b) Nephritis occurring in the course of congenital syphilis—six cases. In three there was albuminuria with casts and scanty red blood corpuscles in the urine and oedema. A fourth had more marked haematuria and slight oedema. The remaining two cases showed signs similar to the first three, but Levy considers that they developed nephritis as a result of treatment for syphilis. All died. (c) Nephritis in the course of an acute infection or nephritis sui generis—six cases. Of these, three followed bronchopneumonia, enteritis or erysipelas. They showed marked albuminuria and oedema and are classed as degenerative in type. All the patients died. Three other cases of nephritis arose spontaneously and were considered to be examples of acute glomerular nephritis. Oedema and albuminuria were less marked and haematuria was more prominent than in the cases of the degenerative type.

Levy concludes that nephritis in infancy is a rare disease. On the other hand, Brown[11], in Toronto, found fourteen cases under eighteen months in 109 cases of nephritis in children over a period of five years. Gray[12] describes a case of nephritis in an infant aged eight and a half months of five weeks duration during which oedema was constantly present. The albumin in the urine measured 10-19 gm. per litre during the last twelve days of life and enough blood was usually present to give a positive reaction to the guaiacum test. Casts were numerous. The Wassermann reaction was negative. At autopsy tubular degeneration was present and doubtful glomerular changes. This case is classified by Gray as nephrotic nephritis.

Osman[13] discusses the effect of large doses of alkali on a child aged eleven months with oedema which appeared fourteen days before admission to hospital. Albumin exceeded 6 gm. per litre. Casts were numerous but no blood was seen. For seventeen days potassium citrate and sodium bicarbonate, 120 grains of each, were given daily. Oedema then disappeared but possibly the gastro-enteritis which developed played a part in depleting the tissues of fluid. Recovery was apparently complete.

Saldun[14] describes a case of lipoid nephrosis in an infant. Oedema was marked and albumin in the urine reached 30 gm. per litre. The presence or absence of haematuria is not indicated. The Wassermann test was negative. Weight was lost during the course of the disease with diminution of oedema. The blood chemistry findings were: total proteins 7·80 gm. per cent., albumin 3·18 gm. per cent., globulin 4·62 gm. per cent., urea 14·0 mgm. per cent., serum calcium 4·9 mgm. per cent., serum phosphorus 5·0 mgm. per cent.; plasma Cl 230 mgm. per cent. Unfortunately

the date of the blood chemistry findings with reference to the degree of oedema is not mentioned. On the development of bronchopneumonia, death occurred with generalized convulsions, seven weeks after the onset of the nephrosis.

Further references to blood chemistry are given in two cases commencing under eighteen months described as acute tubular nephritis (nephrosis) by Wolbach and Blackfan[15]. Insidious onset of anasarca was the main feature. Albuminuria was marked and haematuria absent. The total protein content of the plasma was 5·8 gm. per cent. and 3·2 gm. per cent., and non-protein nitrogen 55·0 mgm. per cent. and 44·0 mgm. per cent. respectively. At the post-mortem examination tubular degeneration was observed. The glomeruli were normal in one case and in the other there were slight changes which were attributed to septicaemia.

Mackay and Johnstone[16], describe a case of lipoid nephrosis of seventeen years' duration starting at the age of one year and four months. Up to the time of death, which was due to streptococcal peritonitis, renal function tests were normal and cardiovascular changes were absent. Ehrich[17], describing the pathology of the same case, found the kidneys large while microscopic examination revealed hyalinization of 50 per cent. of the glomeruli, the others being apparently normal.

Regarding chronic interstitial nephritis, Mitchell[18], in an exhaustive review, says that comparatively few cases have beeen detected in infancy. Apparently the diagnosis is not easy at this age period. He considers the typical picture to be a high non-protein nitrogen with a tendency to low serum calcium and high serum phosphorus, with absence of oedema. Polyuria is present and albuminuria slight. Mitchell points out that the condition arises from kidney insufficiency due to (a) infective processes with or without deformity of the urinary tract, (b) congenital cystic disease of the kidney, or (c) congenital interstitial nephritis. None of the cases under discussion in this paper are of the chronic interstitial type.

Congenital Syphilis.—From a perusal of the literature the impression is gained that there is close causal relationship between syphilis and nephritis in infancy. Spence[5] suggests that the presence of nephritic oedema in an infant should lead the observer to suspect syphilis.

Four of his five cases died and the fifth recovered on arsphenamine injection. Paterson[19] states that syphilitic nephritis is the commonest cause of oedema in infancy but other manifestations of syphilis are frequently present. Boyd's[6] five cases, in which congenital syphilis was present, were clinically indistinguishable from acute mixed nephritis for although the spleen was palpable in all the patients the only other manifestations of syphilis were a rash, present in one case, and positive reactions to Wassermann's test. All these children died. Post mortem, however, well-marked evidence of congenital syphilis was present. Still[7] quotes two cases with both clinical and pathological evidence of syphilis and nephritis. According to Pfaundler and Schlossmann[20] post-mortem examination gives unmistakable evidence of the disease. Spence[5] and Hutchison[21] believe the skin and nasopharyngeal lesions found in congenital syphilis to be the indirect cause of the nephritis. Paterson and Wyllie[8] report three cases with oedema and albuminuria in which the Wassermann reactions were positive. All died. Of the seventeen cases of nephritis in infancy reported by Levy[10] six had congenital syphilis, in two of which he attributes the nephritis to mercurial treatment.

It is evident therefore from the literature that congenital syphilis may be a cause of nephritis in infancy, but conclusive proof has not been adduced that renal oedema, in the absence of manifest signs of lues, is due to syphilis.

Clinical features of present series.

Little can be said of the aetiology of nephritis in infancy from the data given in this paper. In one case infection of the upper respiratory tract

and in two cases of the alimentary tract preceded the nephritis and conceivably may have been causal. Skin lesions were absent and there was no evidence of scarlet fever. The course of the disease was, in the absence of infection, afebrile and the infants were comparatively bright and did not present the features of a toxaemic illness. The urine contained large quantities of albumin and casts. Haematuria would seem to vary in amount with the duration of the illness. It was present in every case on admission. Cardiovascular changes were absent. Blood pressure records, made in only four instances, were of questionable value as the infants invariably cried during the determination. Oedema with ascites was marked in all the cases save one where it was confined to the face and legs.

There is one feature in this small series which appears to be more constant in its occurrence than in the nephritis of older children, namely, the obstinacy of the oedema. The dominating feature was the great reduction of serum proteins and the persistence of oedema and heavy albuminuria; in four cases haematuria completely disappeared and the clinical picture left was that of the nephrotic syndrome. This contrasts with the state of affairs in nephritis of older children in which the persistence of oedema is the exception rather than the rule. This apparently is the feature which gives the nephritis of infancy its grave prognosis, the tendency to infection in all oedematous subjects being well known. Eight of the ten cases showed infection of the respiratory or alimentary tract while in hospital, the ninth developed a double streptococcal orchitis and the tenth a cellulitis.

The oedema, it would appear, is the direct result of lowering of the serum proteins, especially the albumin fraction. Therefore as far as treatment is concerned, it is suggested that our energies should be directed towards producing a return to normal of the serum proteins.

One might also comment on the absence of uraemic signs. In one case generalized convulsions did occur and death followed after a period of coma. In view of the high non-protein nitrogen and phosphorus of the serum and the histological findings in this case of extensive interstitial changes the diagnosis might be one of true uraemia. In no case did the pseudo-uraemic or hypertensive type of convulsions, seen so frequently in acute nephritis in older children, occur.

Syphilis was apparently not a factor. In five cases the Wassermann reaction was negative and at post-mortem in other four no evidence of lues was found. In the tenth case the Wassermann reaction was not done and permission for a post-mortem examination was refused but there was no evidence of congenital syphilis either from the history or from the clinical examination. It would seem therefore that syphilis should not be diagnosed merely from the presence of oedematous nephritis in infancy in the absence of serological or definite post-mortem evidence.

Biochemistry.—The most significant feature of the biochemical changes in this series is the reduction of serum oncotic pressure. Kylin[22] using Pulfrich's refractometer found that till the second year of life serum proteins are lower than in adults. In this study Howe's method as modified by Hawk and Bergheim[22a] was used in estimating serum proteins. The following figures for normals obtained from a series of infants under two years of age with no apparent abnormality save mild rickets, are almost within the normal limit found in adults and are considerably higher than those obtained by Kylin, possibly because no case in this series was below three months old (see table 1).

TABLE 1.

SERUM PROTEIN AND ONCOTIC PRESSURE: NORMAL CONTROLS.

Age.	Number of cases.	Total proteins gm.	Albumin gm.	Globulin gm.	Calculated oncotic pressure mm. Hg.
		Percentage figures.			
3–6 months	6	6·51	4·67	1·84	28·2
6 months–1 year	4	6·76	4·76	1·99	28·9
1 year–1½ years	5	7·53	5·26	2·27	32·1
Under 1½ years	15	6·93	4·90	2·03	29·8
Over 1½ years	20	7·42	5·02	2·39	30·9

In accordance with the view originated by Starling[23] in 1891 one school of thought believes that oedema, other than that associated with acute nephritis or the development of cardiac failure, is due to reduction of the oncotic pressure of the serum. Whereas the normal is about 30 mm. Hg. the critical level at which oedema tends to appear lies between 14 and 21 mm. Hg. as calculated from Govaert's[24] formula. Another factor in the development of oedema is the diminution of the capacity of the serum to hold salt (NaCl) when the serum oncotic pressure falls. Although in acute nephritis the fall in oncotic pressure per se is in the majority of cases too slight in degree to be the cause of oedema yet Van Slyke and others[25] have shown that 30 per cent. of cases of acute nephritis in their adult series had a reduction of serum oncotic pressure below the oedema level. In a recent publication it was shown that a similar tendency existed in 14 per cent. of cases of acute nephritis occurring in children between two and thirteen years of age.[26] Perhaps the most salient feature of this investigation is that the calculated serum oncotic pressure was reduced below the oedema level in

all the infants in whom the serum proteins were estimated (see table 2). In all the patients who recovered it was observed that a return to the normal level occurred as the oedema disappeared. In the other patient permission to obtain a sample of blood after recovery from nephritis was refused but the child was oedema-free and the urine contained no albumin.

TABLE 2.

TEN CASES OF NEPHRITIS IN INFANTS UNDER 18 MONTHS.
INITIAL OBSERVATIONS ON ADMISSION.

Case.	Age in Years.	Oedema.	Gm. per 100 cc. of serum.			Calculated serum onc. pressure mm. Hg.	N.P.N. mgm. per cent.
			Total protein.	Albumin.	Globulin.		
1 J.Mc.D. ...	$\frac{9}{12}$	+ +	3·67	1·80	1·87	12·5	28·0
2 I.G. ..	$1\frac{3}{12}$	+	3·82	2·40	1·42	15·2	29·2
3 A.H. ...	$\frac{7}{12}$	+ +	4·09	1·63	2·46	12·4	27·5
4 S.C. ...	$1\frac{4}{12}$	+ +	4·87	—	—	—	24·1
5 C.G ...	$\frac{4}{12}$	+ +	4·83	1·60	3·23	13·3	50·0
6 G.A. ...	$1\frac{4}{12}$	+ +	4·52	2·92	1·60	18·3	28·5
7 J.N. ...	1	+ +	4·23	1·96	2·27	13·9	36·3
8 E.K. ...	$\frac{7}{12}$	+ +	—	—	—	—	—
9 G.R. ...	$\frac{8}{12}$	+ +	6·78	2·66	4·12	20·4	29·1
10 S.L. ..	$1\frac{1}{12}$	+ +	4·32	2·46	1·85	16·1	65·2
15 normals under	$1\frac{1}{2}$	—	6·93	4·90	2·03	29·8	< 40·0
20 normals over	$1\frac{1}{2}$	—	7·42	5·02	2·39	30·9	< 40·0
Level below which oedema may occur			5·0	2·5	—	14–21	—

In association with infection a high globulin was consistently observed. Leiter[27], and Darrow et alii[28], who induced low serum proteins in dogs by performing plasmapheresis, observed that globulin regenerated earlier and more rapidly than albumin during recovery when serum proteins rose and oedema disappeared. It is therefore possible that the disappearance of oedema following infection is due to the stimulus of infection causing serum proteins to regenerate, a rise in globulin preceding that of albumin.

Non-protein nitrogen was above normal in two cases only, case 5 in whom it reached a level of 50 mgm. per cent., and case 10, 65·2 mgm. per cent. It may be concluded that nitrogen retention is not generally present. In case 5 convulsions appeared a few hours before death and it is possible that uraemia was the cause. Serum phosphorus in that patient reached a level of 7 mgm. per cent. but was not above 5·5 mgm. per cent. in the other cases in which it was estimated. Serum calcium was usually much reduced but in no instance was spasmophilia detected, suggesting that the

reduction was at the expense of the protein-bound fraction which is held to be inert as regards its influence on neuro-muscular excitability (Salvesen and Linder[29]).

Treatment.—Few suggestions of practical value can be put forward. One case recovered without treatment by drugs or diet. A high protein diet was given in one of our patients, case 1. For reasons already given it is doubtful if it was responsible for the return of the serum proteins to normal. At all events since there is seldom evidence of nitrogen retention a diet containing an amount of protein at least adequate for the age should be given and it should be salt free. In order to promote diuresis in acid-producing salt in the form of ammonium chloride was tried in two cases without producing any reduction in oedema. Peters et alii[30] state that in adults where total protein is below 4 gm. per cent. the employment of diuretics is ineffective, and even if diuresis is obtained at higher levels of the serum proteins the tendency to oedema will remain till serum proteins rise. Therefore diuretics are merely palliative.

Pathology—Post-mortem examinations were made in four of the cases. All showed well-marked damage, of acute type, to both glomeruli and tubules. Case 5 in addition showed extensive proliferation of the interstitial tissue and round cell infiltration. These findings give no support to a diagnosis of pure lipoid nephrosis, the condition present being histologically a glomerulo-nephritis.

Summary.

1. Ten cases of acute nephritis in infants under eighteen months of age are reported. The clinical and biochemical findings are described. The disease was characterized by obstinate oedema and a reduction of serum proteins in every case. Seven of the cases were fatal, death being due in five or possibly six cases either to pneumonia or enteritis. In one case death was due to cellulitis. The other three cases made complete recoveries, in one without any special form of treatment. In one high protein diet and in another ammonuium chloride were used, but there was no evidence that recovery was due to these therapeutic measures.

2. There is no evidence that the nephritis was the result of a syphilitic infection.

3. The oedema is ascribed in every case to a fall in the serum protein with consequent reduction in the oncotic pressure. This was a constant finding and the condition differs in this respect from acute nephritis as seen in older children where fall in oncotic pressure below oedema level occurred in only fourteen per cent. Attempts at treatment should be directed towards causing a rise in the serum proteins as the cure is coincident with their return to normal. Spontaneous cure as in older children accounted for all the recoveries.

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INHERITED SMALLPOX

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Most authorities record that the association of pregnancy and smallpox is malign and that abortion, due to uterine haemorrhage, frequently results from it. At the same time it is recognized that inherited infection is commoner in smallpox than in any other acute illness and many references are to be found in the literature to this subject of smallpox in pregnancy and its effect upon the foetus. Schamberg and Kolmer[1] discuss inherited infection and record a few cases. The generally accepted view appears to be that this type of infection is fortuitous and that there is no fixed relation between the onset of the disease as it occurs in the mother and as it may occur in the child. From the literature it is to be gathered that in the later stages of pregnancy the child may be born alive or dead, suffering from smallpox, incubating the disease or having recovered from it in utero. But we have altogether failed to find any favourable reference to time-incidence of attacks as a factor of importance in maternal and foetal smallpox; or, for example, any set of data which would suggest that the incidence of inherited infection may vary in accordance with the stage which the pregnancy has reached when the woman contracts smallpox, or that it may bear some relation to the time-interval between the onset of her attack and the birth of the child.

In an attempt to obtain some more definite information on this aspect of the subject, we have recently analyzed the records of relevant cases which have been under our care in the London smallpox hospitals during the last six years. We have watched many women, at all stages of pregnancy, preserve that state through an attack of smallpox and we have encountered only two who aborted. But we wish to emphasize that the fact that throughout this period all save fourteen patients, none of whom was pregnant, out of a total of over thirteen thousand admitted to hospital, suffered from the results of infection with a benign strain of virus and consequently from modified smallpox, very materially enhanced our opportunities for observation.

Case records.*

Our cases, thirty-four in number, fall into four groups:—

Group 1.—True congenital smallpox.

Case 1.—Onset of mother's illness 20.6.29; rash 22.6.29. Child born 29.6.29, 'rash present at birth'; admitted to hospital 1.7.29; smallpox rash then vesiculo-pustular (about third day); died 2.7.29.

Case 2.—Onset of mother's illness 20.4.31; rash 22.4.31. Child born 29.4.31 (? premature) 'rash present at birth'; admitted to hospital 6.5.31, smallpox rash then 8 or 9 days old; recovered.

Case 3.—Onset of mother's illness 22.2.32; rash 25.2.32. Child born in hospital 6.3.32 with smallpox rash present estimated to be 3 or 4 days old; recovered.

These three cases were born alive at or about full term, and in each case a period of about ten days elapsed between the onset of the mother's illness and the estimated time of appearance of the exanthem on the child. The significance which we attach to this latter point will be referred to in the general discussion.

Group 2.—Inherited infections (type 'A').

Case 4.—Onset of mother's illness 16.2.29; rash 19.2.29. Child born 16.2.29; vaccinated successfully 22.2.29; admitted to hospital 28.2.29; rash appeared 26.2.29, on eleventh day of extra-uterine life and of mother's illness; recovered.

Case 5.—Onset of mother's illness 21.1.30; rash 23.1.30. Child born 21.1.30; admitted to hospital and vaccinated successfully 27.1.30; rash 31.1.30 on eleventh day of extra-uterine life and of mother's illness; recovered.

Case 6.—Onset of mother's illness 26.4.30; rash 29.4.30. Child born 26.4.30; admitted to hospital and vaccinated successfully 1.5.30; rash 5.5.30 on tenth day of extra-uterine life and of mother's illness; recovered.

Case 7.—Onset of mother's illness 27.1.30; rash 29.1.30. Child born 28.1.30; admitted to hospital and vaccinated successfully 31.1.30; rash 8.2.30 on twelfth day of extra-uterine life and thirteenth day of mother's illness: recovered.

Case 8.—Onset of mother's illness 25.4.31; rash 26.4.31. Child born in hospital and vaccinated successfully 30.4.31; rash 7.5.31 on eighth day of extra-uterine life and thirteenth day of mother's illness; recovered.

Case 9.—Onset of mother's illness ? 25.1.34; rash 29.1.34. Child born 25.1.34; rash 3.2.34, i.e., tenth day of extra-uterine life and of mother's illness; recovered.

Case 10.—Onset of mother's illness 7.6.31; rash 8.6.31. Child born in hospital and vaccinated successfully 14.6.31; rash 19.6.31, i.e., sixth day of extra-uterine life and thirteenth day of mother's illness; recovered.

Case 11.—Onset of mother's illness 2.11.30; rash 4.11.30. Binovular twins born in hospital and vaccinated successfully 9.11.30; rash appeared on each twin 14.11.30, i.e., sixth day of extra-uterine life and thirteenth day of mother's illness; recovered.

In this group infection was acquired in utero, or possibly during separation from the parent, and in each case the child's rash appeared within fourteen days of birth. In each case the mother at the time of parturition was either in the pre-eruptive stage of smallpox or in the early days of efflorescence. The common interval of nine to twelve days between the onset of the mother's toxaemia and the appearance of the child's rash is again to be remarked.

* For permission to publish clinical details of these cases we are indebted to Dr. A. F. Cameron, Medical Superintendent of the River Hospitals.

Group 3.—Inherited infections (type 'B').

Case 12.—Onset of mother's illness 12.2.30; rash 14.2.30. Child born (? premature) 16.2.30; admitted to hospital and vaccinated successfully 19.2.30; rash 26.2.30, i.e., eleventh day of extra-uterine life and fifteenth day of mother's illness; died.

Case 13.—Onset of mother's illness 29.3.30; rash 31.3.30. Child (first of binovular twins) born in hospital and vaccinated successfully 6.4.30; rash 16.4.30, i.e., eleventh of extra-uterine life and nineteenth day of mother's illness; recovered. The second (case 25) did not develop smallpox.

Case 14.—Onset of mother's illness 5.6.30; rash 7.6.30. Child born in hospital and vaccinated successfully 7.6.30; rash 18.6.30, i.e., twelfth day of extra-uterine life and fourteenth day of mother's illness; recovered.

Case 15.—Mother successfully vaccinated 24.5.30; rash 4.6.30. Child born 4.6.30; admitted to hospital and vaccinated successfully 6.6.30; rash 14.6.30, i.e., eleventh day of extra-uterine life and thirteenth day of mother's illness; recovered.

Case 16.—Onset of mother's illness 30.7.30; rash 1.8.30. Child born 1.8.30; admitted to hospital and successfully vaccinated 4.8.30; rash 12.8.30, i.e., twelfth day of extra-uterine life and fourteenth day of mother's illness.

Case 17.—Mother vaccinated successfully 8.12.30; rash 9.12.30. Child born 10.12.30; admitted to hospital and vaccinated successfully 13.12.30; rash 21.12.30, i.e., on twelfth day of extra-uterine life and fifteenth day of mother's illness.

The common factors in this group are the appearance of the focal rash in each case on the eleventh or twelfth day of life, and the fact that in each case (with one exception) the child was born actually at the time of outcrop of the mother's focal rash. During the delivery of case 13 the mother's rash was six days old.

Group 4.—Infants born of infected mothers, but who escaped congenital infection.

Some of these acquired smallpox subsequent to birth.

A. Born immediately prior to the onset of the mother's illness.

Case 18.—Onset of mother's illness ? 9.1.31; rash 11.1.31. Child (premature) born 7.1.31; admitted to hospital and vaccinated successfully 13.1.31; did not develop smallpox.

Case 19.—Onset of mother's illness 21.11.32; rash 25.11.32. Child born 18.11.32; admitted to hospital and vaccinated successfully 26.11.32; did not develop smallpox.

B. Born at the onset of the mother's illness.

Case 20.—Onset of mother's illness 14.5.29; rash 16.5.29. Child born 14.5.29; admitted to hospital and vaccinated successfully 18.5.29; did not develop smallpox.

Case 21.—Onset of mother's illness 23.10.29; rash ? 25.10.29. Child born (premature) 23.10.29; not vaccinated; rash 7.11.29; admitted to hospital 9.11.29; died 24.11.29.

Case 22.—Onset of mother's illness 14.11.29; rash 16.11.29. Child born 14.11.29; admitted to hospital and vaccinated successfully 21.11.29; rash 29.11.29; recovered.

Case 23.—Onset of mother's illness 28.4.31; rash 30.4.31. Child born 30.4.31; admitted to hospital and vaccinated successfully 5.5.31; rash 13.5.31; recovered.

Case 24.—Onset of mother's illness 22.6.31; rash 24.6.31. Child born 22.6.31; not vaccinated; rash 7.7.31; recovered.

It is to be observed that those infants who contracted smallpox subsequent to birth developed the focal rash fourteen days after the appearance of the mother's rash, and, further, that these cases either were not vaccinated or were vaccinated late in the incubation period.

C. Born during the first week of the mother's rash.

Case 25.—Onset of mother's illness 29.3.30; rash 31.3.30. Child (second of binovular twins) born in hospital and successfully vaccinated 6.4.30; did not develop smallpox. First twin (case 13), similarly vaccinated, developed smallpox on the eleventh day of extra-uterine life.

D. Born late in mother's illness (after the first week of her focal rash).

Case 26.—Mother's rash 14.10.29. Child born in hospital and successfully vaccinated 21.10.29; did not develop smallpox.

Case 27.—Mother's rash 25.11.29. Child born in hospital and successfully vaccinated 4.12.29; did not develop smallpox.

Case 28.—Mother successfully vaccinated 23.3.30; rash 25.3.30. Child born in hospital and successfully vaccinated 5.4.30; did not develop smallpox.

Case 29.—Mother's rash 12.4.31. Child born in hospital and successfully vaccinated 23.4.31; did not develop smallpox.

Case 30.—Mother's rash 17.7.30. Child born in hospital and successfully vaccinated 31.7.30; did not develop smallpox.

Case 31.—Mother's rash 9.6.30. Child born in hospital and successfully vaccinated 18.6.30; did not develop smallpox.

Case 32.—Mother's rash 24.4.30. Child born in hospital 15.5.30; vaccinated unsuccessfully 15.5.30; vaccinated successfully 20.5.30; did not develop smallpox. This child was fortunate to escape smallpox in that successful vaccination was delayed until the sixth day.

E. Born during the convalescence of the mother and found to be immune from smallpox.

Case 33.—Mother's rash 14.12.29. Child born in hospital 8.1.30; unsuccessfully vaccinated on 8, 10 and 12 January, 1930; did not develop smallpox.

Case 34.—Mother's rash 1.6.29. Twins born 21.7.29; each vaccinated unsuccessfully on three occasions; did not develop smallpox. A description of this case has been given elsewhere (Marsden[2]).

General discussion and conclusions.

While clearly recognizing that any general inferences drawn from the small number of cases which constitute the present series would be unscientific and might even prove to be definitely misleading, we consider that the evidence afforded justifies certain particular conclusions.

In the first place our cases bear out the already well-recognized fact that when both mother and foetus are infected they do not pass through the disease simultaneously, except perhaps in rare instances. In other words, the foetus does not become infected synchronously with the mother but subsequently, and then the foetus passes through an individual period of incubation.

Secondly support is forthcoming for the theory that, as in the case of syphilis, it is, if not exactly fortuitous, more or less of an accident if infection is inherited. All the cases (seventeen) in groups 1, 2 and 3 were infected, whereas those in group 4 (seventeen) escaped. As far as can be seen these cases were at equal risk; with the exception of cases 18 and 19, and possibly of case 9, all were in utero at the onset of the illness in the mother.

Furthermore, it is difficult to explain on any other hypothesis the course of events in cases 13 and 25, binovular twins born on the seventh day of their mother's focal rash, one of whom, successfully vaccinated at birth, developed a smallpox eruption on the eleventh day of extra-uterine life, while the other, similarly treated, remained free from the disease. If, then, it be accepted that in the present state of our knowledge it is impossible to explain what factor, other than chance, determines whether a woman suffering from smallpox shall transmit the infection to her unborn foetus, the interesting question still remains whether the child is at equal risk throughout its mother's attack, or whether there is some stage of her illness, a point of particular danger to the infant, when infection of the foetus is most likely to occur.

As is well known, after infection with the virus of smallpox there follows a latent (incubation) period during which the virus apparently undergoes some proliferative process in the body of the host until, at about the twelfth day, the virus generalizes and symptoms of what is known as the toxaemic stage of smallpox become manifest. Paschen[3] considers that this sudden inundation of the blood with virus shows that primarily one or more lesions giving enormous multiplication of virus must have been created, and that this lesion must lie in the lungs. He points out that, although nobody has yet seen this primary focus, the employment of neurolapine is followed by the production of gross pulmonary lesions. According to the embolic theory, formulated to explain the nature and production of the focal rash, within about twenty-four hours from the point when generalization commences, the blood stream is flooded with infective particles, which, subsequently becoming lodged in the minute capillaries of the skin and certain mucous membrances, give rise to the specific focal lesions. The eruption is known to be determined to certain areas of the body surfaces which, in virtue of their susceptibility to vascular variations, are peculiarly favourable sites for the deposition of the particulate virus, although why this process should be limited to the skin and adjacent mucous membrances is not properly understood.

On general grounds the most likely time for the foetus to become infected would appear to be during the mother's ' septicaemic ' stage, immediately following the onset of her illness. If this be the true method of transference of infection, via the maternal blood stream, we are quite unable to explain why it does not always occur, but we consider that our evidence supports the view. In the vast majority of instances smallpox infection is acquired by way of the respiratory tract and about fourteen days afterwards (sometimes as late as seventeen days and more rarely as early as twelve), the outcrop of the focal rash commences. But however inherited infection is acquired before birth it is plain that it cannot be by way of the respiratory tract, and it is natural to look for some modification of the usual incubation period in accordance with the unusual channel of infection.

Inoculation with smallpox material, variolation of the human subject, was a fairly common procedure in pre-Jennerian times, and records are

available of the course of the disease produced in this manner. Following the appearance on the fourth day at the inoculation site of a local lesion which progressed in a manner similar to that which is adopted by vaccinia, a general focal rash made its appearance usually on the eleventh day. In a case of accidentally inoculated smallpox recently under the observation of one of us the first signs of a general eruption were noted on a day calculated, from evidence supplied by the local lesion, to be the twelfth following inoculation.

It may be that herein lies the clue which we have been seeking and study of the details of cases 1 to 11 reveals a period, between the onset of the mother's illness and the appearance of the focal rash on the child, which closely corresponds to the incubation period of inoculated smallpox. The cases in group 3, all with the exception of number 13 born synchronously with the outcrop of the mother's focal rash, if regarded on the reasonable assumption that they were infected at or about the time of separation (birth) present a similar incubation period. This assumption might legitimately be challenged on the grounds that, as the interval between the onset of the mother's illness and the appearance of the child's rash in the cases which form this group varies from fourteen to eighteen days, it would be equally justifiable to conclude that infection of the foetus had taken place at the commencement of the mother's illness and then had been succeeded by a normal incubation period. We would point out, however, that such a postulate could not be extended to include the cases in groups 1 and 2.

We conclude, therefore, that our evidence suggests that the bulk of foetal infections are acquired in utero at the time of the mother's 'septicaemia' by a process the results of which, particularly in regard to length of incubation period, are akin to those of inoculation (cases in groups 1 and 2). But that if the foetus then escapes it may similarly acquire infection at or about the time of separation from its parent (cases in group 3 and possibly also those in group 2), and that this is particularly liable to occur if the mother's rash is in its early stages when the birth takes place. That if the child escapes these two contingencies it escapes congenital infection; but that generally, and in the absence of prompt successful vaccination, the disease, acquired by the more usual respiratory route, will show itself after the normal period of incubation (cases 21 to 24). And lastly, there is evidence that if the foetus escapes intra-uterine infection and remains in utero until the mother is convalescent from her attack of smallpox, it may then be born immune, at any rate temporarily, from the disease (cases 33 and 34). It is realized, however, that these patients may have survived in utero an attack of smallpox of which they presented no superficial evidence at birth.

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BONE CHANGES IN LEUKAEMIA*

PART I.—CLINICAL AND ROENTGENOLOGICAL

BY

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AND

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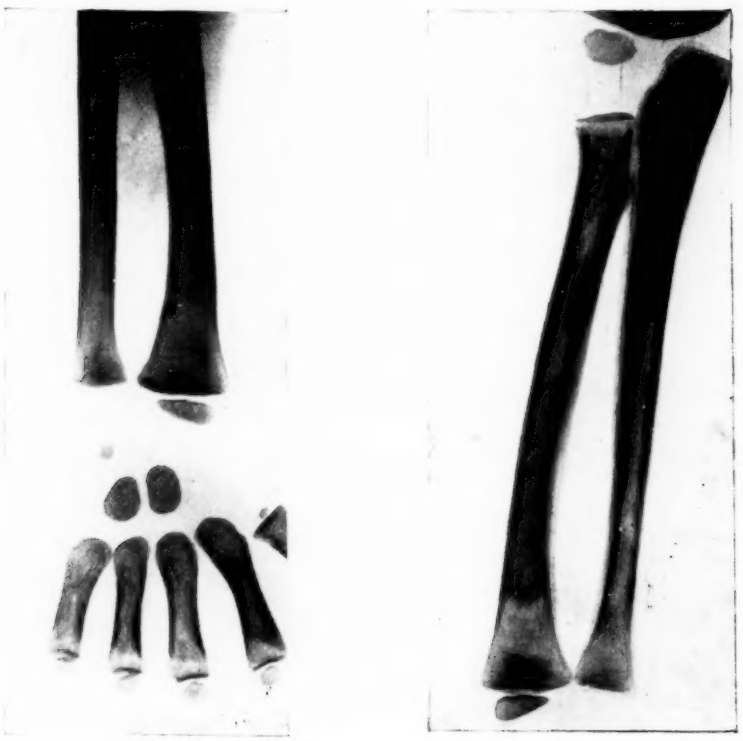
Skiagrams of children with leukaemia have revealed changes in the structure of the long bones. These were observed by us independently, but a search of the literature shows that similar changes have been reported by a few authors. The material for this report is obtained from skiagrams and



A B

FIG. 1. Case 10.—A. Left wrist taken July 25, 1933, shows normal bone configuration. B. Taken Oct. 27, 1933, shows marked rarefaction particularly at the ends of the bones and periosteal elevation of radius and ulna. The same change was seen in the other long bones, particularly the humeri.

* Read at the twelfth annual meeting of the Canadian Society for the Study of Diseases of Children, June 1934.

Case	Age	Sex	History	Spleen and Glands	W.B.C.	Lymphoid. per cent.	Biopsy or P.M.	X-ray findings
1	$2\frac{6}{12}$	F	Pallor, tiring easily	+	2,-20,000	84-90	+	Rarefaction at end of long bones adjacent to epiphyseal line
2	$2\frac{6}{12}$	M	Anæmia, large abdomen	+	33,000	88	+	Same picture as above
3	$3\frac{6}{12}$	M	Glandular enlargement	+	2,500-5,500	75-95	+	At first normal, later same as above
4	2	M	Swelling in neck	+	300,000	99	+	Same picture as above
5	4	F	Epistaxis	+	12,-50,000	60-97	-	Normal on admission, later same as above
6	$3\frac{6}{12}$	M	Joint pains, swelling of joint, epistaxis	+	4,-17,000	92-97	-	Same picture as above
7	$3\frac{6}{12}$	M	Weakness, fever, glandular swelling	+	1,900-6,500	95-100	-	Same picture as above
8	$3\frac{6}{12}$	M	Glandular swelling, pallor, pain in extremities	+	2,-18,000	90-99	-	Same picture as above
9	6	F	Flitting joint pains, fever, twitching hands and face, pallor, irritability	+	3,500	98	+	Rarefaction at ends of bones, thinning of shaft, raising periosteum
10	$2\frac{6}{12}$	M	Pains in joints recurring pallor, swelling of parotid gland	+	1,400-14,000	15-90	+ +	On admission normal, later same as Case 9
11	$\frac{6}{12}$	M	Swelling arms and legs, petechial hemorrhage	+	27,-30,000	86-96	+	Generalized marked change as in Case 9 + a spontaneous fracture of right femur
12	$1\frac{7}{12}$	F	Pain and swelling of arms and legs	+	2,400-26,000	63-96	+	Marked change similar to Case 9

records of twelve cases of lymphatic leukaemia studied in the Hospital for Sick Children, Toronto. Only those details of the laboratory and clinical findings by which the diagnosis was established will be given and these are recorded in the table.

Each of these twelve cases of leukaemia at some stage showed bone changes. Eight showed only a rarefied area at the end of the bone; four showed a periosteal elevation as well. These are all the patients with leukaemia in which we have skiagrams of the bones in various stages of the disease. The age of all patients in this series is below six years, and for the most part, less than four years. Those showing periosteal elevation as well as two of the others, complained of pains in the extremities. The symptoms of this group simulated rheumatic fever, and, in the two younger

patients, scurvy and luetic bone change. The periosteal change might be confused with the picture of luetic bone disease.

Allison[1], in 1924, reported a case of chloroma in a three-year old girl in which there was a raising of the periosteum similar to that seen in congenital lues. The new bone was laid down parallel to the shaft except at the end where it was at right angles. Taylor[2], in 1926, reported a child of two and ten months with leukaemia, with pain and swelling of extremities. Skiagrams of long bones showed elevation of periosteum throughout. Karshner[3] reported a similar case in a child of two years and nine months. Karelitz[4] reports one case of leukaemia and one patient with neuroblastoma that had periosteal elevation.

Poynton and Moncrieff[5] reported two cases of leukaemia which showed a rarefaction at the ends of the long bones, and later Poynton and Lightwood[6] observed a patient who showed periosteal elevation.

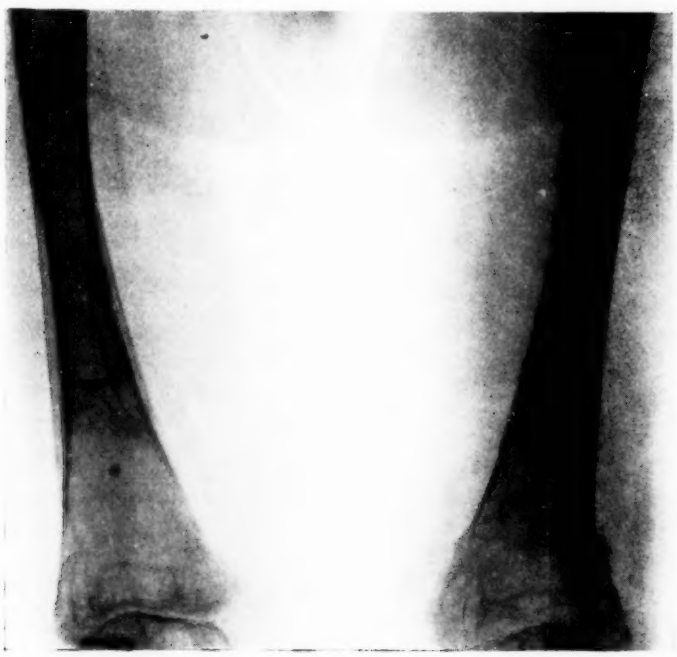


FIG. 2. Case 11.—Both femora show marked rarefaction or decreased density throughout the shaft. There is a raising of the periosteum and a fracture of the left femur as a result of the pathological change.

The other diseases of the blood showing roentgen change in bone are: metastatic new growths with secondary anaemia, marble bones, Gaucher's disease, chloroma, haemophilia, von Jaksch's or erythroblastic anaemia[3,4,6,7,8].

Giles[9] described the various types of non-luetic periosteal bone lesions, including fractures, following osteomyelitis, tuberculosis, typhoid, leprosy, pulmonary osteo-arthropathy, osteitis deformans, rickets, scurvy and bone tumours. He did not mention leukaemia or chloroma.

The radiological examination of the long bones is of value in confirming the diagnosis of leukaemia. If a patient has a suggestive blood picture the examination of the bones may reveal the changes described above. In conditions where the patient has symptoms of rheumatic fever, examination of the blood and the bones are necessary to rule out leukaemia.

Osteomyelitis has also to be kept in mind in the differential diagnosis. One of the patients referred to in the bibliography was operated on as a case of osteomyelitis.

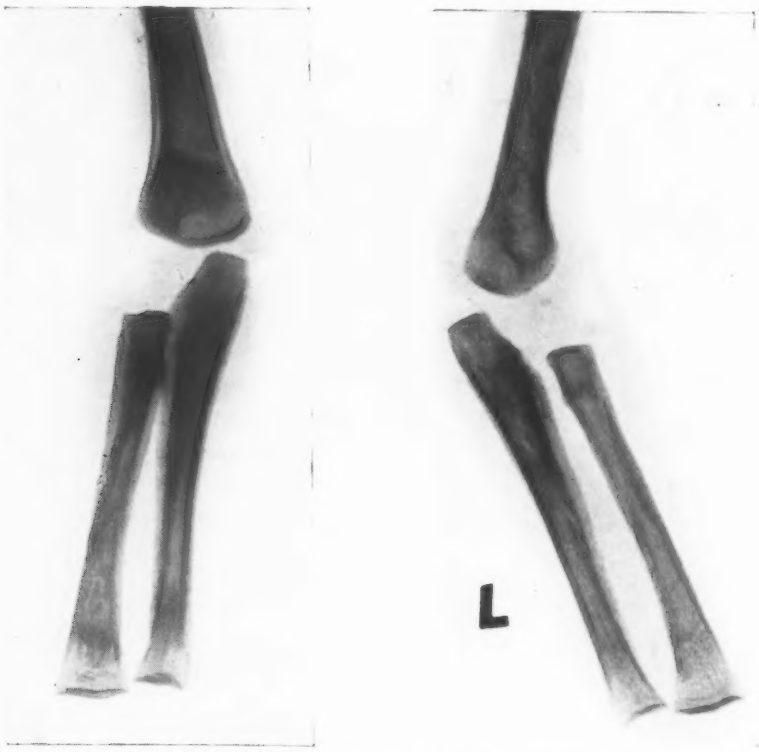


FIG. 3. Case 12.—Lower ends of humerus, radius and ulna on both sides show rarefaction of shaft more marked at ends of long bones and generalized periosteal elevation.

Summary.

The roentgen changes in the long bones of twelve cases of lymphatic leukaemia are given. In eight they consisted of rarefaction across the shaft just adjacent to the epiphyseal line. In four cases there was also a raising of the periosteum.

Flitting joint pains were noticed by six patients prior to admission. All the patients were less than six years of age.

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PART II.—PATHOLOGY

BY

I. H. ERB, M.B.*

The purpose of this communication is to draw attention to the pathological changes which take place in bones in leukaemia, as the result of which the clinical and roentgenological picture as described by Snelling and Brown becomes apparent. While the roentgenological findings have been reported by several authors in recent years, comparatively little has appeared in the literature dealing with the underlying pathology. The subject is dealt with briefly by Smith[1], Taylor[2] and somewhat more fully by Petrassi[3].

The material for this paper was obtained at post mortem from two cases of acute leukaemia dying in the Hospital for Sick Children. Case 1 (case 9 of the clinical series) is that of a girl who died with terminal septicaemia at the age of six years following an illness of nine weeks' duration, the outstanding symptoms of which were shifting joint pains, fever, twitching of hands and face, irritability and increasing pallor. Case 2 (case 10 of clinical series) is that of a boy of two-and-a-half years, who also died with terminal septicaemia, following an illness of six-and-a-half months' duration, in which the chief symptoms were recurring pains in the joints, pallor and swelling in the region of the parotid gland. These were the only cases in the series of twelve reported by Snelling and Brown in which autopsies were obtained. Instead of describing the details of these two cases individually, the findings in the bones in both cases will be grouped under various headings followed by a brief discussion of the relation of these lesions to symptoms.

Bone changes in leukaemia may be grouped under the following headings:—

1. Infiltration. 2. Rarefaction. 3. Proliferation. 4. Degeneration. 5. Haemorrhage.

One or more of these changes may be found in any case of leukaemia and in almost any bone in the body.

I. Infiltration.—By the use of this term in regard to bone changes, we mean simply the deposition of leukaemic cells in bone, be it in the marrow cavity, Haversian canals, or under the periosteum. We do not propose to discuss whether this infiltration is neoplastic or inflammatory, nor do we wish to discuss the question of the origin of these cells. Whatever may be the starting point of this disease, whether in the bone marrow, lymph glands or spleen, abnormal cells soon find their way into the blood stream and are distributed all over the body where they are deposited in various organs and

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where we have reason to believe they continue to multiply. Outside of the bones this infiltration is best seen in such organs as the liver, kidney, testicle, etc.

Wherever this infiltration takes place, these accumulations of cells tend to crowd out the original structures. In the kidney, for example, there may be compression atrophy of both tubules and glomeruli, the more highly specialized structures being damaged the most. The same is true of bone. These cells increase in number at the expense of the bone marrow, which gradually becomes crowded out (fig. 1) resulting in secondary anaemia, which

FIG. 1. Case 2.—Rib: extensive infiltration with leukaemic cells in marrow cavity. H. & E. × 60.

is progressive. Not only do these infiltrating cells fill the marrow spaces, but they spread into the Haversian canals and ultimately may reach the periosteum. Here they may multiply between the periosteum and cortex of the bone, the periosteum becoming elevated as the cells increase in numbers.

2. Rarefaction.—As the process of infiltration increases, not only is the bone marrow crowded out, but many of the bone trabeculae also disappear. Whether this is simply a pressure atrophy caused by the marked increase in the numbers of leukaemic cells, or whether these cells produce an osteolytic enzyme, we are not prepared to say. At any rate, the trabeculae disappear at irregular intervals throughout the shaft of the long bones, and it is this

rarefaction which is one of the first evidences of pathological change to be visualized by x-ray. One common site for this rarefaction is at the epiphyseal line. Here, not only may the trabeculae disappear, but the normal architecture of the columns of cartilage cells is also greatly altered (fig. 2).

As the disease progresses and more and more cells invade the Haversian canals, these canals enlarge at the expense of the adjacent compact bone until there may remain only a shell of honeycombed bone between the periosteum

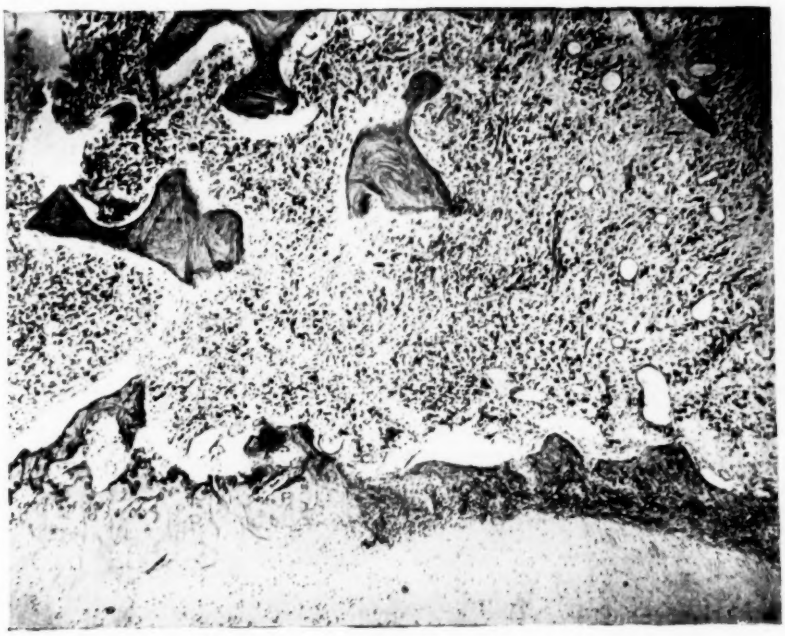

FIG. 2. Case 2.—Humerus at distal epiphyseal line. The normal architecture of both cartilage columns and bone trabeculae is greatly altered. Many of the latter have disappeared entirely. H. & E. × 36.

and what was originally the marrow cavity (fig. 3). This process of rarefaction may progress to such an extent that spontaneous fracture may result as shown by Snelling and Brown. This, however, was the only case in the series in which this complication arose, and no such fracture has so far been observed at a post mortem in this department.

3. Proliferation.—While the processes of infiltration and rarefaction may occur in almost any bone, and at almost any site in the bone, the formation of new bone is apparently limited to the subperiosteal region. The stimulus responsible for this new bone formation seems to be the separation of the periosteum from the cortex of the bone by reason of the invasion of leukaemic cells underneath the periosteum, these cells having arrived there by way of the Haversian canals. It is not necessary to assume that these leukaemic cells possess any bone-forming stimulus themselves, since it is well known that such laying down of new bone may follow stripping up of the periosteum from any cause whatever. Familiar examples are seen

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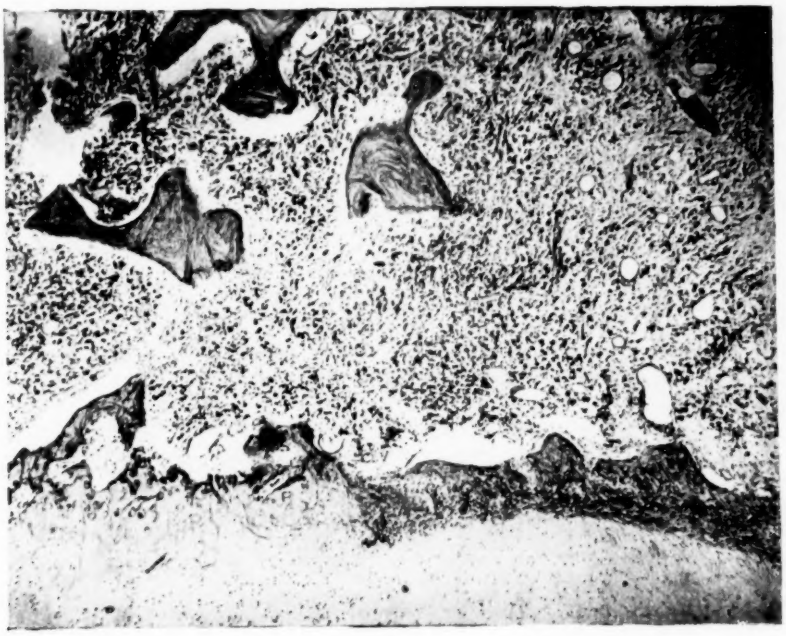

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following subperiosteal haemorrhages in scurvy and cephalhaematomata, and and also following periosteal elevation in osteomyelitis. Another example less frequently seen is that of adrenal neuroblastoma with bone metastases. In a recent case (the details of which are shortly to be published), the periosteum of the skull was elevated in places to a distance of 5 cm. and in the underlying tumour mass were numerous spicules of bone radiating outward from the surface of the skull. A somewhat similar picture is described by Karelitz[1] in discussing periosteal elevation. In leukaemia we have observed this new bone formation in the humerus, femur, fibula, ribs and sternum, although radiological evidence of such proliferation in other bones is by no means lacking.

FIG. 3. Case 2.—Humerus: widened Haversian canals filled with leukaemic cells. H. & E. × 36.

In some instances the general tendency is for the trabeculae of new bone to lie perpendicular to the shaft, while in other instances, they appear to have no definite arrangement (fig. 4, 5).

Under the heading of proliferation, mention should also be made of the development of new bone marrow in some of the subperiosteal inter-trabecular spaces. This was observed between the dura mater and skull in case 1 (fig. 6, 7, 8). Here the inner surface of the skull was traversed by numerous fine ridges of new bone, while the spaces or grooves between these ridges were filled with bone marrow. This extra-cortical bone marrow may represent a response to a demand for new blood-forming tissue in an attempt to replace that lost by the extensive infiltration by the leukaemic cells of the great bulk of the original marrow cavities of many of the bones.

4. **Degeneration.**—In some of the long bones the masses of leukaemic cells are prone to undergo degeneration. This is seen on gross examination in the form of yellowish foci of greater or less extent in the marrow cavities. Microscopically in these areas of degeneration the shadows of the cells can still frequently be discerned. The explanation of this degeneration probably lies in the interference with the blood supply as the result of pressure on blood vessels from the increasing number of leukaemic cells.

5. **Haemorrhage.**—Just as haemorrhage is prone to occur in other organs infiltrated with leukaemic cells, as for example, in the kidney, so it may occur in bone. It is the presence of these foci of haemorrhage alternating with yellowish areas of degeneration and reddish-grey areas of masses of living leukaemic cells that gives to the cut surface of the medullary cavity of a long bone the striking mottled appearance sometimes seen.

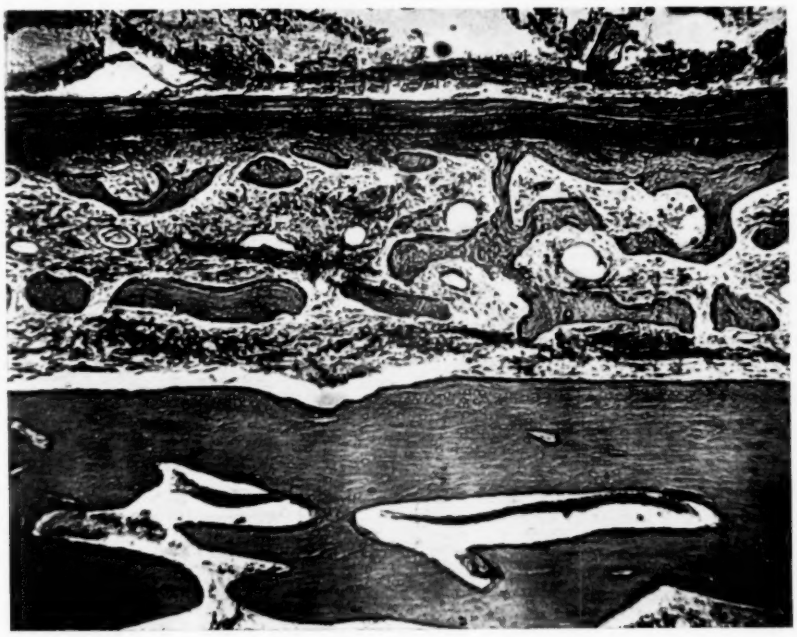

FIG. 4. Case 2.—Humerus: subperiosteal new bone. H. & E. × 36.

Comment.

Of the changes described above, the most important from the clinician's point of view are the first three. The last two, namely degeneration and haemorrhage are of little clinical significance. Infiltration with leukaemic cells we believe to be of importance because of the relation which it probably bears to the symptom of pain in the extremities. Whether these cells are inflammatory or neoplastic, their presence in such enormous numbers must result in increased pressure within the bone, a condition somewhat akin to that of a tumour within the skull giving rise to headache. In this connection the clinical article illustrates the frequency with which the symptoms simulate those of acute rheumatic fever. Pain in the legs was also mentioned by

Karelitz[1] in his case of neuroblastoma with metastases into the bones of the legs. Some idea of the extent to which leukaemic infiltration may progress may be obtained from our records of another case of leukaemia. This was that of a boy who died at four-years-and-nine months, after an illness of five-and-a-half months. In this case the combined weight of the kidneys was 1,124 gm., approximately ten times their normal size. All this increased weight was contained within the kidney capsule which had gradually stretched to accommodate the increase in leukaemic cells. On section of these kidneys there was marked eversion of the cut edges indicating increased tension on the capsule.

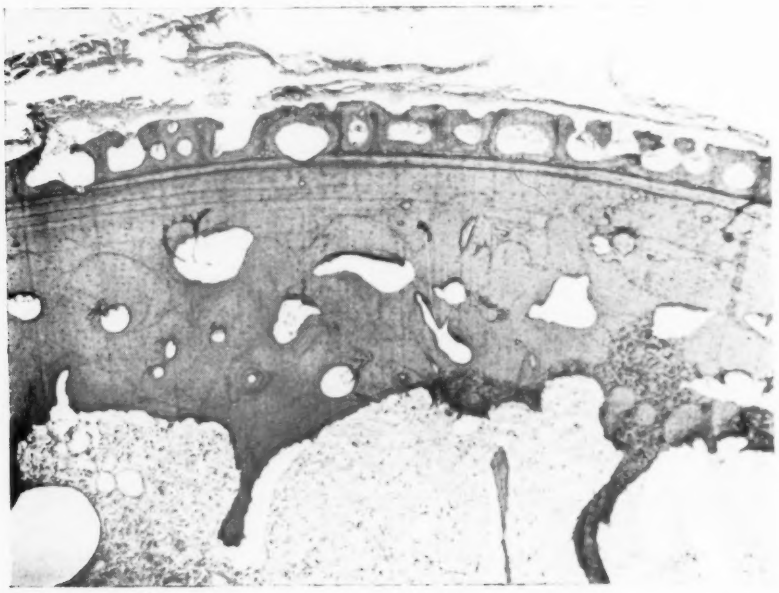

FIG. 5. Case 1.—Rib: the subperiosteal new bone is becoming more dense. H. & E. × 36.

In bone, on the other hand, no such stretching is possible so that increased pressure must result. Whether this pressure is within the marrow cavity, the Haversian canals, or under the periosteum may matter little, except perhaps that in the latter situation the bones might be more tender on pressure. In any case pain in the extremities is a common complaint in cases of this type. That the symptom of pain may be referred to the joints without any evidence of pathological change within the joint itself may be explained on the basis of the close relationship between joint ligaments and periosteum.

The relation between replacement of bone marrow by leukaemic cells and the profound anaemia which is usually present requires little comment. Case 1 is of particular interest in view of the evidence of development of extra-medullary marrow between the dura mater and the inner table of the skull. This obviously represents an attempt to supply the demand for blood which is not being formed in its normal site.

While the process of infiltration we believe to be closely related to the symptom of pain, it cannot be visualized in the skiagrams. The changes which may thus be recognized are those of rarefaction on the one hand and

FIG. 6. Case 1.—Section through whole thickness of skull showing numerous ridges of new bone inside the inner table. The dura was stripped off in removing the calvarium. H. & E. × 2.

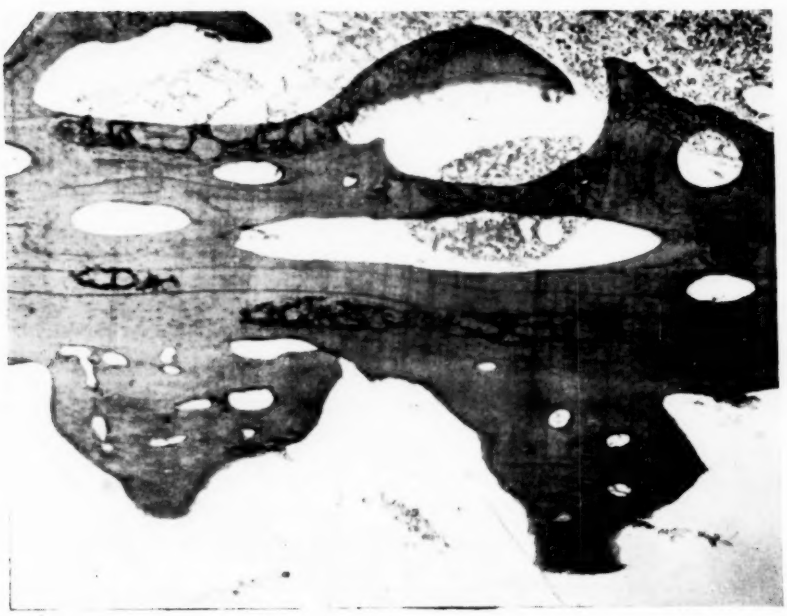

FIG. 7.—Higher magnification of small area in fig. 6. × 36.

subperiosteal proliferation of new bone on the other hand. Although we have had opportunity to study the tissues of only two such cases, nevertheless we believe that the process of rarefaction always precedes that of proliferation and for this reason it may be visible skiagraphically before there is any

evidence of new bone formation. As pointed out in the clinical paper, one common site for this rarefaction to make its appearance is at the epiphyseal line but it may be seen anywhere throughout the shafts of the long bones.

FIG. 8. Case 1.—Section of dura showing ridges of new bone marrow. These lay between the bony ridges shown in fig. 7. H. & E. × 30.

Summary.

The changes in bone in acute leukaemia in childhood may be grouped under the following headings: Infiltration, rarefaction, proliferation, degeneration, haemorrhage. These changes are illustrated by two cases of leukaemia, one, a girl, dying at the age of six years, the other, a boy, dying at the age of two-and-a-half years.

Infiltration with leukaemic cells may occur in bone as it does in the liver and kidney or elsewhere and may involve the marrow cavity, Haversian canals or subperiosteal region. By replacing bone marrow it may give rise to profound anaemia. It is not visible on x-ray examination.

Rarefaction occurs chiefly towards the ends of the long bones, but may occur anywhere along the shaft and involve both cancellous and compact bone. Spontaneous fractures may result.

Proliferation of new bone occurs underneath the periosteum following elevation of the periosteum by infiltrating leukaemic cells. This new bone is demonstrable by x-ray examination as are also the areas of rarefaction.

Degeneration of masses of leukaemic cells, as well as haemorrhage into the marrow cavity may occur in the course of the disease, but these changes are of little clinical significance, except perhaps to add to symptoms of toxaemia.

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For further literature see references in Part I.

THE GASTRIC SECRETION IN NORMAL AND RHEUMATIC CHILDREN

BY

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The object of the present investigation was to determine whether the gastric secretion in children is influenced by certain diseases. The results obtained from gastric analyses in normal children and in those suffering from various manifestations of rheumatism are described.

Gastric secretion in healthy children.

Before considering the gastric secretion in disease it seemed advisable to determine the variations in health and to what degree these were influenced by age, for there is considerable difference of opinion on these points.

It is generally accepted that the gastric secretion is influenced by several factors such as age, general condition and psychological response of the individual, as well as by certain diseases. Although most of these conclusions have been obtained from work done on the gastric secretion in adults, several investigators have shown that they apply also to infants and young children.

Klementsson[1] states that there is an increase in acidity which reaches its maximum between four and seven years and remains about that level for the remainder of childhood; while Vanzant, Alvarez, Eusterman, Dunn and Berkson[2] show that there is a rapid increase up to twenty years after which the acidity decreases to old age. They also show that at puberty males have higher acidity than females and that the frequency of achlorhydria increases from youth to old age. It is a well-known fact that a certain proportion of otherwise healthy normal adults have no free hydrochloric acid, but whether this happens in children is doubtful. Muhl[3], in examining forty healthy children from one to thirteen years, found none with achlorhydria and only one with hypochlorhydria. Chievitz[4] also never found congenital achylia in healthy children, although in infants under one year of age the acidity was lower than in adults and older children. Klementsson[1] discusses the possibility of congenital achylia and does not consider that there is any convincing evidence of its occurrence. Griswold and Shohl[5] found that even in the very young infant free hydrochloric acid is present in the gastric secretion and record a pH value of 2·6 as early as one hour after birth.

The type of stimulus used has a very definite effect on the gastric response as some 'fix' the acid more than others. It is recognized that histamine gives a maximum stimulation and has the advantage of giving a clear juice which is secreted so rapidly that duodenal regurgitation does not occur (Klumpp and Bowie[6]). Neutral 7 per cent. ethyl alcohol is also made use of by some workers but in children it has the disadvantage of not being a usual constituent of the diet. This disadvantage is pointed out by Deitrich and Shelby[7] who compared the results obtained from a test meal of shredded wheat biscuits and one using 7 per cent. ethyl alcohol.

* This work was done during the tenure of a Muirhead Scholarship and a McCunn Medical Research Scholarship.

Although Wills and Paterson[8] found that with various types of milk feeds there was an increase in gastric acidity with those of high buffer value they concluded that the response depended more on the general condition of the child than on the nature of the feed. They also showed that the gastric juice of breast-fed infants had a higher pH and that the stomach emptied more quickly than in those artificially fed. That the milk content of the previous diet has no influence on the gastric secretion was shown by Chievitz[1].

The question of the effect of duodenal regurgitation on the gastric acidity has given rise to many conflicting statements. Davison[9] has shown that only about one-third of all specimens in children are free of either salivary or duodenal contamination. Morrell Roberts[10] considers that regurgitation is normal in man and takes as evidence of its occurrence a fall in acidity with a corresponding rise in inorganic chlorine and little or no change in the total chlorine and considers that any difference is due to dilution only. Bolton[11] also holds that regurgitation is a normal occurrence and that defective neutralization may be due to insufficient relaxation of the pylorus.

On the other hand Shay, Katz and Schloss[12] consider that the duodenal contents are never sufficiently alkaline to affect the gastric acidity to any great extent and that indeed the pancreas would have difficulty in secreting such a quantity. McLean and Griffiths[13] think that the gastric acidity is regulated by the concentration of acid and that if regurgitation occurred there would be an increase in the amount of trypsin and in the CO_2 content of the gastric contents which is only the case when bile is present. Indeed they, with Williams[14], find in isolated gastric pouches in dogs that the acidity varies as in the normal stomach. Copeman and Hill[15] have studied the analyses of fractional test meals in fifty normal children and find that, whereas free and total acid varied considerably, even in the same individual, the total chlorine was much more constant, and therefore is a better index of the gastric secretion. They therefore suggest that a modified curve could be obtained by omitting the initial fall due to the ingestion of food and plotting the fasting and hourly values for the total chlorine, and that this curve would give a very good indication of gastric secretion and would obviate the fallacies of the presence of saliva and of duodenal regurgitation. The acidity of a sample depends on the level at which it is obtained, and it follows that any regurgitation will affect the acidity at the pyloric end of the stomach, while it may have little or no effect on the total amount of juice. Duthie[16] has shown that there is an appreciable difference in the acidity of the juice obtained from the pyloric portion and that obtained from the cardiac. He found that the greatest difference was present when bile was obtained from the pyloric tube, showing that regurgitation had occurred. If the tube is kept at the same level throughout the test, this should have little effect on the changes during digestion. Ylppo[17] found that by producing fever with hot baths, etc., the gastric acidity is lower than normal. Fever produced by injection of foreign protein, causes a fall in gastric acidity for as long as the fever lasts. He suggests that this may have a connection with summer diarrhoea and the gastro-intestinal symptoms at the commencement of any acute parenteral injection.

Present investigation.—An attempt has been made to determine the effect of age on the gastric secretion of healthy children. As the children were all in the Sick Children's Hospital the number of healthy individuals was comparatively small. They were all convalescent from the diseases with which they had been admitted to hospital and were generally tested just prior to discharge.

The examinations were carried out in the morning after the night's fast, and blood was taken before the test meal was given. The fasting gastric juice was then removed by means of a fine Ryle's tube and strained porridge given in amounts varying with age. Thereafter samples were withdrawn every 15 minutes for 2 hours, except in young children who would not retain the tube, and in these, samples were removed every half hour. The samples of gastric contents were then centrifugalized

and the supernatant fluid examined. Free and total acidity were estimated by titration with $\frac{N}{10}$ NaOH, using dimethylaminobenzol and phenolphthalein as indicators. A modification of Van Slyke's method was used to determine the chlorine of the gastric juice and of the blood. An index of the peptic activity was obtained by measuring in millimetres the amount of egg white digested in Mett's tubes after incubation for 24 hours at 37°C. In some of the later cases the pH of each specimen was estimated by means of the B.D.H. capillator apparatus. Cases with a very high or very low acidity were generally re-examined and if achlorhydria was still found an injection of 0·15—0·28 c.c. of 1/1000 histamine phosphate was given. The iodine-starch reaction was used as an indication of the time at which the stomach was empty of porridge.

Owing to the wide individual variations in the acidity of the gastric contents the patients were divided into age periods each of three years and the average maximum values obtained and compared. The results are given in table 1. From this and fig. 1 it will be seen that there is an increase in

TABLE 1.

GASTRIC ANALYSES OF NORMAL CASES.

Age in years.	No. of cases	Averages of maximal values in each age group.						No. of cases	Total chlorine of fasting blood c.c. $\frac{N}{10}$
		Free HCl c.c. $\frac{N}{10}$	Total acidity c.c. $\frac{N}{10}$	Total chlorine c.c. $\frac{N}{10}$	Peptic activity units.	pH			
						Fasting	Max.		
0— 3	12	22·7	43·9	75·9	51·1 (9)*	4·2	2·2	21	73·7
3— 6	19	30·0	46·0	79·2	48·1 (11)*	3·5	2·0	18	73·7
6— 9	15	31·4	50·7	77·1	32·4 (1)*	3·0	2·8	15	73·9
9—12	14	41·0	60·4	87·7	—	—	—	14	73·1

* Figures in brackets indicate number of cases.

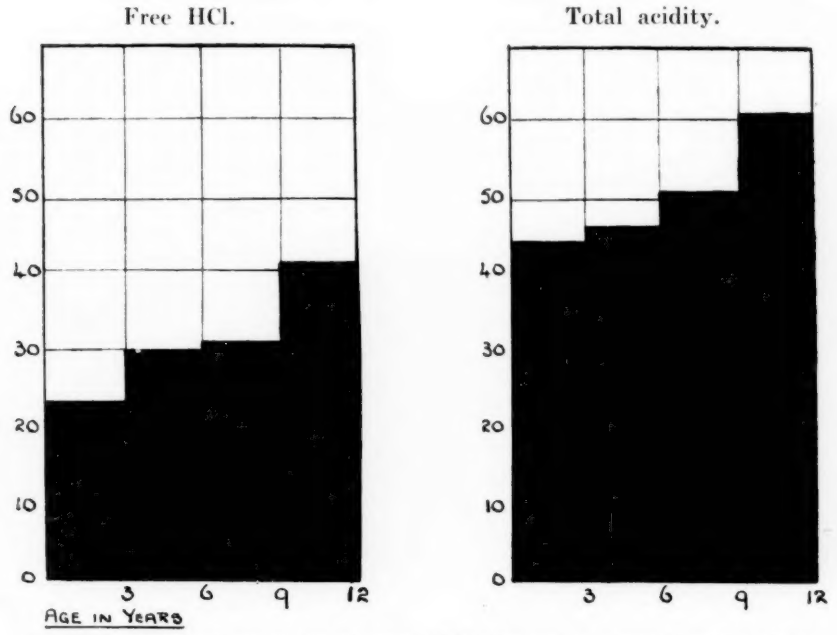

FIG. 1.—SHOWING INCREASE IN FREE HCl AND TOTAL ACIDITY WITH AGE.

the average maximum free and total acidity with age. This is statistically significant when non-adjacent groups are compared but is not apparent when adjacent groups are examined. The pH of the fasting juice also showed an increase with age, while the average maximum pH showed no significant difference in various age periods.

The total chlorine of the gastric juice also showed an increase with age but this is only significant when the youngest and oldest groups are compared.

The peptic activity was very variable. Twenty-one children were tested and in eight (38 per cent.) the curve for peptic activity ran parallel with the total acidity curve, while in five (23·8 per cent.) it followed the curve for inorganic chlorine. In the remainder it appeared to be independent of any of the other curves. The time at which the maximum activity occurred varied but in eight (38 per cent.) it was highest in the fasting specimen and in four (19 per cent.) at two hours. This is in agreement with McLean, Griffiths and Hughes[18] who have shown that peptic activity increased towards the end of secretion and is generally highest in the resting juice. In several cases of the present series the peptic activity curves showed more than one peak.

After this summary of the results of the gastric analyses the individual cases may be studied more particularly. In all, 60 were examined, 38 being girls and 22 boys, their ages ranging from 5 months to 12¼ years. The free and total acidity generally ran parallel to each other, while the total chlorine, after the initial fall on the ingestion of the meal, rose to a fairly constant figure, following the acidity but at a higher level. When the acidity fell due to excess of mucus or the presence of bile, the total chlorine generally remained high but if the fall in acidity was due to lack of secretion the chlorine fell also. Eight cases (13 per cent.) had hyperchlorhydria having more than 50 per cent. free HCl in terms of $\frac{N}{10}$ alkali. Two cases showed hypochlorhydria having less than 12 per cent. free acid; one case had achlorhydria when first tested but on being retested a week later the free acid was found to reach a maximum of 20·3 per cent. Fifty children (82 per cent.), therefore, had gastric acidity within normal limits taking 20–40 per cent. as normal for free acid; 40–60 per cent. for total acidity in terms of $\frac{N}{10}$ alkali and 60–90 millieq. per litre for total chlorine.

The emptying time was determined by the starch-iodine reaction and in the normal cases 63 per cent. gave a negative reaction at two hours, while 37 per cent. still gave a blue colour with iodine in the two hours specimen. If anything the emptying time was shorter in boys than in girls.

From table 1 it will be seen that the average total chlorine of the blood is constant for all the age groups. The total chlorine of the blood and fasting gastric juice tend in most cases to be in about the same concentration: in some, however, the blood chlorine was high when the gastric chlorine was low and vice versa. In a series of twenty other children the total chlorine of the fasting blood was compared with that of blood taken forty-five minutes after a test meal and there was found to be practically no difference.

The results found in normal children show that with age there is a definite increase in the acidity and total chlorine of the gastric secretion

and that this is evident up to 12 years of age. The peptic activity appears to be higher in the younger children but the numbers are too small for satisfactory comparison. Duodenal regurgitation did not appear to occur except when the stomach was almost empty or when there was severe retching.

Gastric analysis in rheumatic conditions.

The recent view that the manifestations of rheumatism have an allergic basis suggested that a study of the gastric secretion in patients suffering from this disease might show some departure from normal similar to that found in recognized allergic conditions.

Bray[19] has shown in his recent work on the allergic child that in asthma and similar conditions there is an increase in the frequency of hypochlorhydria and achlorhydria compared with normal. In discussing the possible allergic explanation of the rheumatic syndrome he mentions the chronic arthritis often seen in individuals with other allergic phenomena and likens it to a giant urticaria. He quotes Poynton and Schlesinger[20] who show by analogy, experiment and clinical evidence that rheumatism is similar in its manifestations to other allergic conditions. They also mention the low gastric acidity which is obtained in cases of chronic arthritis.

If this hypothesis is correct one would expect to find a higher percentage of cases with hypochlorhydria and achlorhydria among those with rheumatism than among non-rheumatic subjects. To test this the gastric secretion of a series of patients with manifestations of acute rheumatism was examined and compared with results obtained from the group of children of the same age described in the previous section.

All the children examined were afebrile and convalescent, especially those with chorea and all were over three years except one of two years and nine months who for convenience was included in the youngest group. The average maximum figures over periods of three years were taken as in the first part of this paper.

Ninety-nine children were examined, 68 girls and 31 boys and the figures obtained are shown in Table 2. It will be seen that in the three–six years

TABLE 2.

GASTRIC ANALYSES OF RHEUMATIC CASES.

Age in years.	No. of cases.	Averages of maximal values in each age group.				No. of cases	Total chlorine of fasting blood c.c. $\frac{N}{10}$
		Free HCl c.c. $\frac{N}{10}$	Total acidity c.c. $\frac{N}{10}$	Total chlorine c.c. $\frac{N}{10}$	Peptic activity units.		
0— 3	—	—	—	—	—	—	—
3— 6	12	23·5	43·9	78·7	102·4 (1)*	12	75·1
6— 9	36	37·6	55·6	85·4	69·2 (11)*	38	74·9
9—12	51	43·8	60·0	79·2	90·9 (17)*	58	69·9

* Figures in brackets indicate number of cases.

period the average maximum for free and total acid and total chlorine is lower in the rheumatic than in the normal cases, while over six years the figures are higher in rheumatism. The differences are small and not statistically significant.

The peptic activity appears to be higher in the rheumatic group but the numbers are too small for comparison.

The average total chlorine of the fasting blood is similar to the normal in each age period.

Examining the results in more detail 24 patients were found to have hyperchlorhydria; that is 24 per cent. as compared with 13 per cent. of the normals. Of these, 15 were girls and 9 were boys; 15 were cases of chorea (6 with cardiac disease) and 9 of rheumatic fever (8 with cardiac disease). Hypochlorhydria was present in seven of the rheumatic cases and all were girls, six with chorea and one with rheumatism. Five cases had achlorhydria, three boys and two girls. Two of the boys had chorea and one rheumatism, while one girl had chorea and one rheumatism. One of the boys on being retested was found to have free acid but low in amount, another on a second test had a fair quantity. The girl with chorea gave a normal histamine response. The girl with rheumatism was retested after tonsillectomy and she was found to have 23·4 per cent. free hydrochloric acid. The boy with rheumatism appeared to have a complete achylia; in six test meals over a period of six months no free acid was found and the total acidity, the chlorine and the peptic activity were low even with histamine. Ventriculin and large doses of iron improved his mild anaemia and general condition without having any effect on his gastric secretion.

The remaining 63 cases (63 per cent.) were within average limits as against 82 per cent. of the normals, so that although there is no significant difference in the average figures for gastric secretion of rheumatic and normal children the former show more variation with a larger number of extremes (table 3).

TABLE 3.

THE INCIDENCE OF ABNORMAL GASTRIC SECRETION IN HEALTHY AND RHEUMATIC CHILDREN.

	Percentage of total.			
	Within normal limits.	Hyper-chlorhydria.	Hypo-chlorhydria.	Achlorhydria.
Normal (60 cases) ...	82	13	5	0
Rheumatic (99 cases)...	64	24	11	1

The emptying time was much the same as for normal children; 35 per cent. showed a starch reaction at two hours while in 65 per cent. starch could not be detected at this period. As in the non-rheumatic cases boys showed a more rapid emptying rate than girls, but a much larger number of the latter were tested.

Fifty-one of the rheumatic cases were skin tested with antigen prepared from streptococci (haemolytic and non-haemolytic). The bacterial extracts were made according to the method employed by Collis[21]. It was found that

seven of the forty-one children sensitive to streptococci had hyperchlorhydria, three had hypochlorhydria and four achlorhydria but no connection was discovered between the severity of the skin reaction and the gastric response. One boy with normal gastric secretion, who had a sharp reaction with tachycardia and adenitis twenty-four hours after the skin test, was given another test meal at that time, that is when presumably he was having an allergic reaction. The gastric analysis gave practically identical results to those found previously. Of thirteen non-rheumatic children who reacted to streptococcal antigen, one had hyperchlorhydria and the others had a gastric secretion within normal limits.

A review of the results obtained in the rheumatic patients shows that 12 per cent. had either hypochlorhydria or achlorhydria against 5 per cent. of the normal. This suggests that there may be an allergic factor associated with acute rheumatism in childhood. There seems to be no connection between the severity of the skin reaction to streptococcal antigen and the type of gastric analysis obtained.

I desire to thank Professor G. B. Fleming and Dr. N. Morris for suggesting this investigation and for their helpful criticism. I also wish to acknowledge the gift by Messrs. Parke, Davis & Co. of the histamine phosphate used in the cases referred to in this paper.

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